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AMEBIASIS AMONG THE AMERICAN ARMED FORCES IN THE MIDDLE EAST

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INTRODUCTION

THE RECENT American literature [1] has been placing increasing emphasis on the probability that American armed forces located in tropical and subtropical areas will return to the United States harboring many diseases acquired in these localities. A report of the Office of War Information [2] listed dysentery as the second greatest threat of disease among American overseas forces. Malaria headed the list.

This report covers the experience of a general hospital of the United States Army, located in the Middle East, with respect to amebic infection, during the period between Nov. 11, 1942, and Nov. 31, 1944. The present war is the first time that American troops have been stationed in this region in any considerable numbers. Amebiasis is hyperendemic in this area, principally because of the policy of using human feces as fertilizer. The host-parasite relationship, and thus the clinical picture, will not be similar in the native population and in our troops. As Faust [3] has pointed out, a host-parasite equilibrium develops in a population after long exposure, while fresh groups introduced into an endemic area will not have acquired a similar equilibrium and will therefore have a higher incidence of symptoms and a more manifest clinical picture.

From the Gastrointestinal Section, 38th General Hospital, United States Army Forces in the Middle East.

1. (*a*) Mackie, T. T.: Tropical Diseases: A Postwar Health Problem, New York State J. Med. **43**:1509-1513 (Aug. 15) 1943. (*b*) Wright, W. H.: Present and Post-War Health Problems in Connection with Parasitic Diseases, Science **99**:207-213 (March 17) 1944.

2. Health of the Armed Forces, J. A. M. A. **123**:487 (Oct. 23) 1943.

3. Faust, E. C.: Some Modern Conceptions of Amebiasis, Science **99**:45 (Jan. 21) 1944.

INCIDENCE

The incidence of amebiasis has been reported by authors from various parts of the world. Sapero and Johnson [4] found an incidence of 14.7 per cent among the United States Naval recruits from the Southern states and an incidence of 7.8 per cent among those from the Northern states. Wenrich [5] reported an incidence of 4.1 per cent among 1,060 college freshmen, while Rothman and Laskey [6] reported an incidence of 3.6 per cent in a survey of the staff of the Graduate Hospital of the University of Pennsylvania, Philadelphia, Strong [7] quoted Craig's report (1937) in which he found that of 57,561 persons examined in twenty-six different surveys in the United States an average of 10.2 per cent were found to harbor Endamoeba histolytica. Stitt [8] stated that, of nearly 7,000 British troops and civilians without any history of intestinal trouble examined in the Eastern Mediterranean area during World War I, 10.5 per cent were found infected with E. histolytica, while of 31,000 British troops returning to England from the Near East, the majority of whom had dysentery or other intestinal disturbances, 9.8 per cent were found infected. Bulmer and Priest,[9] reporting from a British General hospital in the Middle East, stated that, from March 1941 to September 1942, 4,178 patients with diarrheal diseases were admitted, 1 per cent of whom were infected with E. histolytica. Wright [1b] quoted a British report stating that about one eighth of the men hospitalized for dysentery cases in North Africa were infected with E. histolytica.

In an attempt to determine the incidence among the native population, in July 1943 we made microscopic examinations of suspensions in warm saline solution of the normally evacuated feces of 50 native workmen. All specimens were cultured in an attempt to determine the presence of pathogenic intestinal bacteria. The results of this examination are summarized in table 1.

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4. Sapero, J. J., and Johnson, C. M.: Endameba Histolytica and Other Intestinal Parasites: Incidence in Variously Exposed Groups of the Navy, U. S. Nav. M. Bull. **37**:279-287 (April) 1939.

5. Wenrich, D. H.; Stabler, R. M., and Arnett, J. H.: Endamoeba Histolytica and Other Intestinal Protozoa in 1,060 College Freshmen, Am. J. Trop. Med. **15**:331-345 (May) 1935.

6. Rothman, M. M., and Laskey, M.: Survey of Protozoan Infection of the Staff of a Large General Hospital, Am. J. M. Sc. **206**:369-371 (Sept.) 1943.

7. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 6, Philadelphia, The Blakiston Company, 1942, vol. 1, p. 477.

8. Strong,[7] p. 476.

9. Bulmer, E., and Priest, W. M.: Bacillary Dysentery: Chemotherapy in Its Treatment, Lancet **2**:69-71 (July 17) 1943.

One or more parasitic organisms were found in 90 per cent of the workmen. E. histolytica was present in 22 per cent, while 46 per cent harbored more than one organism. Since, as Faust [10] stated, only 20 to 25 per cent of cases of infections with E. histolytica are diagnosed by examination of a single direct fecal film, it is felt that this figure of 22 per cent is conservatively low. In a further attempt to investigate this situation, 25 Sudanese food handlers, whose stools showed no E. histolytica on routine microscopic examination, were given 30 cc. of a saturated solution of magnesium sulfate, and the purged stools were examined. Twelve, or 50 per cent of these, were found to harbor E. histolytica. By means of the technic of examining suspensions of the purged stool in warm saline solution, 167 Italian prisoners of war were examined prior to their acceptance as mess personnel. In 36, or 21.6 per cent, E. histolytica was found.

In the 38th General Hospital 77 members of the mess personnel, all

TABLE 1.—*Organisms Found on the Examination of the Feces of Fifty Native Workmen*

Organism	Patients	Per Cent
Ascaris lumbricoides	26	52.0
Endamoeba histolytica	11	22.0
Ancylostoma duodenale	11	22.0
Trichomonas hominis	7	14.0
Strongyloides stercoralis	4	8.0
Trichostrongylus colubriformis	2	4.0
Giardia lamblia	2	4.0
Schistosoma mansoni	2	4.0
Blastocystis hominis	1	2.0
Shigella paradysentery group	5	10.0
More than one organism	23	46.0
None	5	10.0

of whom were American soldiers, had purged stools examined each month during the entire period covered by this report. Of these, 28, or 36.4 per cent, were found to harbor E. histolytica on one of the examinations. In none of these 28 men was the organism found until the organization had been in this locality for approximately one year. Twenty-two, or 70.5 per cent, were entirely free of symptoms. Since routine examinations of purged stools were not performed on the entire personnel of the orginzation, it is not known whether this increased incidence among the food handlers was followed by an increased incidence among the remainder of the personnel.

Examination was made of either a purged stool or sigmoidoscopic washings of all of the members of the 38th General Hospital who complained of abdominal symptoms. Of the entire organization, 12 of 60 officers, or 20 per cent, 29 of 138 nurses, or 21 per cent, and 103 of 618

10. Faust, E. C.: Some Modern Conceptions of Amebiasis, Science **99**:69 (Jan. 28) 1944.

enlisted personnel, or 16.2 per cent (or a total of 144 of 816 personnel, or 17.8 per cent), were found to be suffering from symptomatic infection with E. histolytica during the two year period. This does not include the 22 food handlers without symptoms.

During the period covered by this report, 1,596 patients with enteric infections were admitted to the hospital. Of these 464, or 27.9 per cent, were infected with E. histolytica. Since all patients admitted to the hospital with intestinal dysfunction were examined for E. histolytica by the previously described technic, it is felt that relatively accurate figures were obtained so far as the hospitalized patients were concerned. However, due to the transient status of a considerable portion of the soldier population, no statistically accurate figures could be compiled for the entire population. My colleagues and I feel that the previously quoted incidence among the hospital personnel is a more or less accurate picture of the entire population. Using only those organizations which were permanently stationed in this area, we found that the admission rate for both patients with symptomatic forms of the disease and carriers was higher the second year than the first year. It is felt that this was due to the fact that a longer period of exposure increases the rate of incidence until an equilibrium is eventually established. The highest admission rate occurred in April and May of the second year. This is in agreement with the observations of Simon in the Gulf States, as quoted by Strong.[11] No correlation was found to exist between the rate of admission and the monthly variations in mean relative humidity. This is not in agreement with Strong's [11] statement that the seasonal variation is associated with variations in humidity.

PATHOLOGY

Since an understanding of the pathology of amebiasis is essential for a clinical appreciation of the disease, the highlights of the pathologic changes which occur will be discussed. In this brief résumé, Faust's [3] description of the lesions as they occur in the kitten, an animal easily infected experimentally, has been generally followed. The trophozoites, which are ingested, are killed by the gastric juices, while the cyst forms pass into the small intestines. If the condition of the small intestines, particularly the hydrogen ion concentration, is favorable, excystation occurs. Invasion of tissue by the newly formed trophozoites may or may not occur, depending on the motility of the intestinal canal and the amount of food present. An excessive amount of food prevents the organisms from coming into contact with the mucous membrane of the intestinal canal. Invasion of tissue usually occurs at the first point of stasis in the intestinal canal, the ileocecal region, although the organisms may be swept to the sigmoid region before penetration occurs. They may, at

11. Strong,[7] p. 495.

times, pass completely through the anus without attachment. The site of highest incidence of penetration is the ileocecal region and the ascending colon, with the rectosigmoid region next in incidence, while the middle segment of the colon is rarely involved. The amebas penetrate the mucous membrane by means of a proteolytic ferment. There is a constant reparative process occurring simultaneously with the destructive process. This destructive-reparative balance is influenced by many factors, among which the following are the most important: first, the virulence of the organisms; second, the type of food in the intestinal canal, Hegner and Eskridge [12] having shown that a diet high in carbohydrates favors multiplication of the amebas while a diet high in animal protein retards their multiplication; third, secondary bacterial invasion which lowers the resistance of the local tissue, and fourth, the degree of host resistance based on group immunity, groups newly arriving in an endemic area having a higher incidence of symptoms and a more manifest clinical picture than the permanently resident population.

The pathologic process, and thus the clinical picture, in any given case is the result of this destructive-reparative balance. At times the lesions may be confined to the mucous membrane with extrusion of the organisms and complete healing, or there may be only the formation of shallow, microscopic ulcerations. After invasion of the mucous membrane there is first a lateral spread before penetration into the submucosa occurs. If the first lodgment is at the side or base of the crypt, there may be considerable erosion before hemorrhage occurs; if it is at the tip of the crypt, there is early contact with the capillaries and early hemorrhage. After the penetration of the submucosa there may be lateral spread and the formation of a bottleneck lesion with a small opening into the intestinal lumen, the typical amebic lesion. There is no leukocytic response to this early lesion. Following this, there may be extensive ulceration with gangrene of the wall of the bowel or there may be penetration to and through the peritoneum. There may be penetration of the intestinal mucosa and spreading to other organs, principally the liver and brain. It must be emphasized that penetration of the amebas through the intestinal mucosa and spreading to other organs may occur without any demonstrable intestinal lesion and without any history of intestinal dysfunction.

SIGNS AND SYMPTOMS

As shown in table 2, the patients in this series have been divided into the following types: those with acute amebiasis, 49.2 per cent, who had no history preceding that which was the cause of admission;

12. Hegner, R. W., and Eskridge, L.: Influence of Carbohydrates on Intestinal Protozoa in Vitro and in Vivo, Am. J. Hyg. **21**:121-134 (Jan.) 1935; Elimination of Amoeba from Rats with a High Protein Diet, J. Parasitol. **23**:105-106 (Feb.) 1937.

those with chronic amebiasis, 12.9 per cent, who had a history of symptoms preceding the attack which led to admission; carriers, 26.1 per cent, who had no symptoms at any time; those with concurrent bacillary and amebic infections, 11.4 per cent, and those admitted because of complications of the disease which, in this series, consisted only of hepatic abscesses, 0.4 per cent.

Table 3 shows the clinical picture at the time of admission to the hospital. No symptoms were present in 26.5 per cent of the patients; 35.7 per cent had mild signs and symptoms, consisting of fatigability, mild abdominal pain and either loose stools with a frequency of less than 5 per twenty-four hour period or normal stools; 13.4 per cent were severely ill, with toxicity, dehydration, elevation of temperature, nausea, vomiting and pronounced diarrhea, and the remaining 24.4 per

TABLE 2.—*Types of Patients*

Type	Number	Per Cent
With acute amebiasis	228	49.2
With chronic amebiasis	60	12.9
Carriers	121	26.1
With mixed infections (amebic and bacillary)	53	11.4
With hepatic abscess	2	0.4
Total	464	100.0

TABLE 3.—*Severity of Signs and Symptoms at Time of Admission*

Signs and Symptoms	Number	Per Cent
Lacking	123	26.5
Mild	166	35.7
Moderate	113	24.4
Severe	62	13.4

cent fell between these extremes and were classified as moderately ill. Thus, 62.2 per cent of the patients had either mild signs and symptoms or none at the time of admission.

The number of stools per twenty-four hour period, at the time of admission, is listed in table 4. There was no diarrhea in 41.8 per cent of the patients; 33.8 per cent had less than 5 stools per twenty-four hour period; 18.1 per cent had between 6 and 15 stools; 5.2 per cent had between 16 and 25 stools, and 1.1 per cent had over 26 stools per twenty-four hour period. The highest frequency was 50 stools, which occurred in 1 case. The majority of the patients with acute and chronic amebiasis had less than 5 stools per twenty-four hour period, while the majority of the patients with mixed infections had moderate diarrhea. Only patients with acute amebiasis had severe diarrhea. Moderate or severe diarrhea was not a characteristic in this series, as 75.6 per cent of the patients either did not have diarrhea or had less than 5 stools per twenty-four hour period.

As demonstrated in table 5, most of those patients who were clinically classified as severely ill at the time of admission had diarrhea to some degree. Of these, 43.5 per cent had less than 5 stools per twenty-four hour period while only 6.5 per cent had severe diarrhea.

Abdominal pain, usually mild and cramplike in character, was, as shown in table 6, the most consistent feature in the series, being experienced by 76.7 per cent of the patients with acute amebiasis, 81.6

TABLE 4.—*Number of Stools, per Twenty-Four Hour Period, at the Time of Admission*

Number of Stools per Twenty-Four Hours	Total		With Acute Disease		With Chronic Disease		Carriers		With Mixed Infections		With Hepatic Abscess	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
1	194	41.8	47	20.5	14	23.4	121	100	10	18.9	2	100
2-5	157	33.8	104	45.7	35	58.2	0	0	18	34.0	0	0
6-15	84	18.1	58	25.5	7	11.7	0	0	19	35.8	0	0
16-25	24	5.2	14	6.1	4	6.7	0	0	6	11.3	0	0
Over 26	5	1.1	5	2.2	0	0.0	0	0	0	0.0	0	0
Total	464	100.0	228	100.0	60	100.0	121	100	53	100.0	2	100

TABLE 5.—*Number of Stools per Twenty-Four Hours of Severely Ill Patients*

Stools per Twenty-Four Hours	Number of Patients	Per Cent
1	6	9.7
2-5	21	33.8
6-15	19	30.7
16-25	12	19.3
Over 25	4	6.5

TABLE 6.—*Incidence of Abdominal Pain and Tenderness*

Type Patient	Abdominal Pain		Abdominal Tenderness	
	Number	Per Cent	Number	Per Cent
With acute amebiasis	175	76.7	122	53.0
With chronic amebiasis	49	81.6	25	41.6
Carriers	0	0.0	0	0.0
With mixed infections (amebic and bacillary)	41	77.3	34	64.1
With hepatic abscess	2	100.0	2	100.0
Total	267	57.5	183	39.4

per cent of the patients with chronic amebiasis, 77.3 per cent of the patients with mixed infections and both of the patients with amebic hepatitis. It was present in 57.5 per cent of all patients, and it was experienced by approximately two thirds of the patients admitted with symptoms. In the hepatic abscesses the pain was located in the right upper quadrant of the abdomen while in the others it was located in either or both of the lower abdominal quadrants.

Abdominal tenderness, as shown in table 6, was present in 53.0 per cent of the patients with acute amebiasis, 41.6 per cent of the patients with chronic amebiasis, 64.1 per cent of the patients with mixed infections and both of the patients with hepatic abscess, or 39.4 per cent of all the patients. Thus, abdominal tenderness was present in approximately one half of those patients admitted with symptoms. In the cases of hepatic abscess the tenderness was located in the right hypochondrium. In 25, or 13.1 per cent of the patients with abdominal tenderness, or 5.3 per cent of all patients, the tenderness was most pronounced in the right lower quadrant of the abdomen, producing a clinical picture suggestive of appendicitis.

As shown in table 7, an elevation in temperature to between 100 and 104 F. was not an outstanding characteristic, as it occurred in only 20.6 per cent of the patients with acute disease, 13.3 per cent of the patients with chronic disease and 33.9 per cent of the patients with

TABLE 7.—*Incidence of Systemic Reactions—Elevation of Temperature and Leukocytosis*

Type of Patient	Elevation of Temperature (100-104 F.)		Leukocytosis (10,500-15,000)	
	Number	Per Cent	Number	Per Cent
With acute amebiasis	47	20.6	33	14.4
With chronic amebiasis	8	13.3	6	10.0
Carriers	0	0.0	0	0.0
With mixed infections (amebic and bacillary)	18	33.9	13	25.5
With hepatic abscess	0	0.0	0	0.0
Total	73	15.7	52	11.2

mixed infections, or 15.7 per cent of all patients. A leukocyte count between 10,000 and 15,000 was made for only a small percentage of the patients, 14.4 per cent of the patients acutely ill, 10.0 per cent of the patients chronically ill and 25.5 per cent of the patients with mixed infections, or 11.2 per cent of all the patients whose cases were reported.

Table 8 compares the patient's statement with the actual appearance of the stool with respect to the presence or absence of mucus and blood. Every stool in this series was examined by two persons, one of us and one member of the laboratory personnel. Of the patients with acute disease, 66.1 per cent, and of the patients with chronic disease, 56.6 per cent, showed neither mucus nor blood, while 85.2 per cent of the patients with acute disease and 78.4 per cent of the patients with chronic disease stated that they saw neither mucus nor blood. It is felt, therefore, that both the patient's statement and the gross appearance of the stool are of only limited value and are not diagnostic.

As shown in table 9, sigmoidoscopic examination was performed on 43.5 per cent of the patients with acute disease, 65.0 per cent of the

patients with chronic disease and 26.4 per cent of the carriers. This percentage was not due to any selection of cases but to the fact that there were no electric bulbs procurable for the instrument for a period of time. The wall of the bowel appeared normal in 10.1 per cent of the patients acutely ill, 10.2 per cent of the patients chronically ill and 75 per cent of the carriers. This figure is not surprising if one recalls that the involvement may be only in the cecal region and ascending colon. The wall of the bowel was acutely involved in 29.3 per cent of the patients with acute disease and 20.5 per cent of the patients with chronic disease. It was moderately involved in 60.6 per cent of the

TABLE 8.—*Gross Appearance of the Stool*

Type of Patient	Mucus		Mucus and Blood		Normal	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
With Acute Amebiasis						
Patient's statement	10	4.5	24	10.3	194	85.2
Actual appearance	36	15.8	41	18.1	151	66.1
With Chronic Amebiasis						
Patient's statement	8	13.3	5	8.3	47	78.4
Actual appearance	16	26.7	10	16.7	34	56.6

TABLE 9.—*Sigmoidoscopic Examination*

Appearance of the Wall of the Bowel	Patients with Acute Amebiasis		Patients with Chronic Amebiasis		Carriers	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Normal	10	10.1	4	10.2	24	75
Acutely involved	29	29.3	8	20.5	0	0
Moderately involved	60	60.6	13	33.3	0	0
Scarred	0	0.0	14	36.0	8	25
Total examined	99	43.5	39	65.0	32	26.1

acutely ill and 33.3 per cent of the chronically ill patients. Those walls of the bowel classified as acutely involved appeared definitely inflamed, edematous, friable and discretely ulcerated; those classified as moderately involved exhibited discrete pinpoint ulcerations with relatively normal mucosa intervening. Of the patients with chronic disease 36 per cent, and of the carriers 25 per cent, showed scarring and pitting, the residuals of previous activity of the amebas. All of the patients with mixed infections showed a generalized inflammation of the wall of the bowel, due, probably, to the concomitant bacillary infection. In all cases showing acute involvement the clinical picture was severe. However, 2.5 per cent of those patients who appeared acutely ill had a normal-appearing wall of the bowel. Thus, in 132 of the 170 cases examined, or 78.9 per cent, there were suggestive sigmoidoscopic observations.

Since it is felt that a certain proportion of the American armed forces returning to the United States from endemic areas overseas will be suffering from chronic amebiasis, the prominent symptoms of this group are listed in table 10. The objective observations have been previously enumerated. It will be seen that 78.3 per cent of the group gave a history of intermittent diarrhea with occasional periods of constipation. The diarrhea, in most cases, consisted of periods of loose stools of two to three days' duration accompanied by mild, generalized abdominal pains without any periods of severe watery diarrhea. Those patients who gave no history of diarrhea complained of intermittent pain in the lower part of the abdomen, fatigability and pain in the lower part of the back.

As mentioned by Faust,[10] because of the higher incidence of involvement of the cecal and appendicular regions in tropical and subtropical areas, in many cases amebiasis is confused with appendicitis, and the

TABLE 10.—*Signs and Symptoms of the Patients with Chronic Amebiasis*

Signs and Symptoms	Number		Per Cent	
Intermittent diarrhea and constipation (Forty days to three years)		47		78.3
No diarrhea		13		21.6
Intermittent abdominal pain	11		18.2	
Pain in the lower part of the back	1		1.7	
Fatigability	1		1.7	
Abdominal pain		46		76.6
Anorexia		23		38.3
Malaise		21		35.0
Generalized aches and pains		11		18.2
Headache		5		8.3

patients operated on. He quoted Ochsner's report that 10 per cent of those in whom appendectomy was done at the Charity Hospital, New Orleans, had amebic involvement and the report of the Santa Tomas Hospital, Panama, of a 33 per cent frequency in the patients coming to operation for appendicitis. During the period covered by the present report, 273 appendectomies were performed at this hospital. Nine patients, or 3.2 per cent, had amebic involvement. Six were operated on and E. histolytica was subsequently discovered. Two were given a diagnosis of acute appendicitis at the operating table and the other 4 a diagnosis of enterocolitis. The other 3 were first treated for amebiasis and later operated on because of persistent pain and tenderness in the right lower quadrant. One of these, by barium sulfate enema, has shown a deformity in the region of the cecum, which operation revealed to be because the omentum was densely adherent to the medial wall of the cecum, probably the result of erosion of an amebic ulceration with "walling off" by the omentum. Histologic examination revealed chronic fibrinous appendicitis in the other 2. In one of the

9 cases was E. histolytica observed on microscopic examination of the tissues. We feel that in all cases in which acute appendicitis cannot be definitely ruled out, even if E. histolytica is discovered, a laparotomy should be performed, as the patient may have both amebiasis and appendicitis or there may be erosion of an amebic ulceration in the cecal region.

DIAGNOSIS

As emphasized throughout the literature, the only method of diagnosis is to find the causative organism, E. histolytica, in the feces. As shown in this report, the history, the physical examination, the sigmoidoscopic examination and the gross appearance of the feces were found to be only suggestive. Any or all of these may be normal. One must suspect amebiasis in every one who has resided in an endemic area, particularly if there is a history of vague abdominal pain, fatigability and loose stools alternating with normal stools.

Lincicome,[13] by examination of every stool of infected rhesus monkeys, and Tsuchiya,[14] by daily examination of the stools of a human carrier, have shown that there is a cyclic passage of the cysts of both E. histolytica and E. coli. James [15] summarized the situation when he stated, "It is . . . truly remarkable to see the variations in the number of amebas. . . . On one day the amebas will occur in great numbers and are easily found. On another day they will be uncovered only by a prolonged search in permanent preparations, and the fresh specimen will often be entirely negative." Svensson and Linders [16] recommended the rotuine examination of 10 successive specimens, while Dobell [17] recommended the examination of 6 successive specimens before pronouncing a given person free of the disease. Faust [10] stated that there is a 25 per cent chance of finding the organism in one normally evacuated stool of a person who is known to harbor it.

We feel that the examination of rectal washings obtained by means of a sigmoidoscope, while yielding a high percentage of positive results, cannot solely be relied on, as the infection may be limited to the cecal

13. Lincicome, D. R.: Fluctuation in the Numbers of Cysts of Endamoeba Histolytica and Endamoeba Coli in the Stool of Rhesus Monkeys, Am. J. Hyg. **36**:321-337 (Nov.) 1942.

14. Tsuchiya, H.: Observations on "Encystment Cycle" of Endamoeba Histolytica in a Carrier, Proc. Soc. Exper. Biol. & Med. **29**:930-932 (May) 1931.

15. James, W. M.: Diagnosis of Intestinal Amebiasis, J. A. M. A. **89**:1469-1472 (Oct. 29) 1927.

16. Svensson, R., and Linders, F. J.: The Chances of Detecting Infections with Intestinal Protozoa: A Parasitological Study and Statistical Survey, Acta med. Scandinav. **81**:267-324, 1934.

17. Dobell, C.: Amoebic Dysentery and the Protozoological Investigation of Cases and Carriers, Medical Research Committee, report no. 4, London, His Majesty's Stationery Office, 1917, p. 1.

region and the ascending colon, in which case the sigmoidoscopic findings may be normal. Likewise, cultural methods are reliable only in a positive sense, as excystation may not occur, while the complement fixation test is still of questionable value.

The diagnostic routine used in this series has consisted in the immediate microscopic examination of a suspension in warm saline solution of both the liquid stool and the sigmoidoscopic washings. Lugol's iodine stain has been utilized in the differentiation of the amebic cysts. If the patient did not have a liquid stool, and there were no contraindications, he was given 30 cc. of a saturated solution of magnesium sulfate in the morning, and the second liquid evacuation was examined. Three purged stools which were free of the organism, on three successive mornings, were required before the patient was pronounced either not infected or cured. By means of this technic, 71.6 per cent of the diagnoses of amebiasis were made by finding the trophozoites, 20.4 per cent by finding the precystic form and 8.0 per cent by finding the cystic forms of E. histolytica.

TREATMENT

Although there is some controversy as to whether or not the carriers, or so-called cyst passers, should be treated, all the patients in this series in whom E. histolytica was found were treated irrespective of the presence or absence of symptoms. This includes all the food handlers who were found to harbor E. histolytica as well as the hospitalized patients who were found to harbor the organism on routine examination. We are of the opinion that all are actual or potential sources of infection with the disease. The host-parasite equilibrium may be disturbed by many factors, among which are superimposed general or enteric infections and nutritional changes. There is also the likelihood that the disease may spread to other organs without any evidence of intestinal dysfunction for, as Craig [18] and Johnson [19] have pointed out, invasion of the tissue occurs in all cases, irrespective of the symptoms.

Depending on the availability of the amebicidal drugs, patients with acute and chronic amebiasis and patients with mixed infections were treated by one or the other of three plans of therapy. The patients with mixed infections received either sulfaguanidine, 3.5 Gm. every four hours for a total of 120 Gm., or sulfadiazine, 1 Gm. every four hours for a total of 30 Gm., concurrently with the amebicidal drugs with no ill effects.

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18. Craig, C. F.: The Pathology of Amebiasis in Carriers, Am. J. Trop. Med. **12**:285-299 (July) 1932.

19. Johnson, C. M.: Observations on the Natural Infections of Endamoeba Histolytica in Ateles and Rhesus Monkeys, Am. J. Trop. Med. **21**:49-61 (Jan.) 1941.

The preferred plan of therapy consisted in the single daily intramuscular administration of 0.064 Gm. of emetine hydrochloride for six days with the concurrent oral administration of 0.25 Gm. of carbarsone three times a day for seven days. Following this, 0.6 Gm. of Diodoquin (5,7 diiodo-8-hydroxy-quinoline) was given orally three times a day for seven days.

The alternate plans of therapy, employed from the eighth to the fourteenth day of treatment, when Diodoquin was not available, consisted in the administration of either carbarsone, 0.25 Gm. twice daily, or chiniofon, 1 Gm. three times a day.

Diodoquin, which is nontoxic, was preferred to the prolonged administration of carbarsone, which has all the toxic properties inherent in any arsenical. Carbarsone was preferred to chiniofon because of the irritant action of the latter on the wall of the bowel, resulting in increased diarrhea and abdominal discomfort in 36 per cent of those patients treated with it.

As the margin between the therapeutic and the toxic dose of emetine hydrochloride is narrow, all the patients were kept at complete rest in bed, except for bathroom privileges, for the entire period of administration of the drug and for the succeeding two days. This routine was enforced in the expectation of diminishing the toxic effect of emetine hydrochloride on the myocardium. Daily cardiac auscultation was performed, and the blood pressure was recorded five minutes before and thirty minutes after the administration of the drug. Together with the emetine hydrochloride, 0.010 Gm. of thiamine hydrochloride was given intramuscularly, in an attempt to counteract the cardiac effects of the emetine hydrochloride. A bland diet, low in residue, high in animal protein and low in carbohydrate, was given, as Hegner and Eskridge [12] have shown that this type of diet retards the multiplication of the endameba. If a liquid diet was given, it was changed as rapidly as possible to a bland diet.

The carriers, or so-called cyst passers, were treated by one of the previously described plans of therapy, modified by the administration of emetine hydrochloride for only three days. Although emetine hydrochloride is not universally used in treating carriers, we used it because various authorities (Craig,[18] Johnson [19]) state that invasion of tissue occurs in all cases. In our experience, 25 per cent of carriers, examined sigmoidoscopically, showed petechial scarring of the mucosa of the bowel, evidence of previous activity and invasion of tissue. It was our opinion, therefore, that carriers deserved the benefit of therapy with emetine hydrochloride.

If a patient continued to harbor E. histolytica after any of the previously mentioned plans of therapy, he was given a cleansing enema of 2 per cent sodium bicarbonate solution followed by a 200 cc. retention

enema of 2 per cent carbarsone in 2 per cent sodium bicarbonate solution for five consecutive mornings.

Table 11 lists the patients treated by each of the previously mentioned plans of therapy. Emetine and two courses of carbarsone were given to 252, or 54.3 per cent, of the patients; emetine, carbarsone and Diodoquin to 174, or 37.6 per cent; emetine, carbarsone and chiniofon to 37, or 7.9 per cent, and carbarsone alone to 1, or 0.8 per cent.

TABLE 11.—*Patients Treated by Each Plan of Therapy*

Type of Patient	Emetine Hydrochloride Carbarsone		Emetine Hydrochloride Carbarsone Diodoquin		Emetine Hydrochloride Carbarsone Chiniofon	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
With acute amebiasis	119	52.4	90	39.4	19	8.2
With chronic amebiasis	29	48.4	25	41.6	6	10.0
Carriers *	72	59.5	44	36.4	4	3.3
With mixed infections (amebic and bacillary)	30	56.6	15	28.2	8	15.2
With hepatic abscess	2	100.0	0	0.0	0	0.0
Total	252	54.3	174	37.6	37	7.9

* One carrier (0.8 per cent) received carbarsone alone.

TABLE 12.—*Unsatisfactory Results of Therapy*

Result	Emetine Hydrochloride Carbarsone		Emetine Hydrochloride Carbarsone Diodoquin		Emetine Hydrochloride Carbarsone Chiniofon		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Total number of patients	252	54.4	174	37.6	37	8.1	463	100.0
Stool contained organism after one course; patient cured by second course	4	1.5	1	0.5	0	0.0	5	1.08
Recurrence of disease after patient had been discharged is cured by second course	4	1.5	1	0.5	0	0.0	5	1.08
Patient returned to United States	1	0.4	3	1.7	1	2.7	5	1.08
Patient persistently infected	0	0.4	0	0.0	0	0.0	1	0.22
Patient had chronic colitis	0	0.0	3	1.7	1	2.7	4	0.86
Total	9	3.4	5	2.7	1	2.7	15	3.23

Table 12 lists those patients who, in our opinion, did not respond satisfactorily to a single course of therapy. Of all the patients treated, 15, or 3.3 per cent, fell into this category. Of those treated with emetine hydrochloride and two courses of carbarsone, 5, or 1.9 per cent, continued to pass E. histolytica after the completion of therapy. Four of these 5 cleared after a second course of therapy. The fifth patient continued to pass E. histolytica after two courses of emetine hydrochloride and carbarsone followed by retention enemas. This patient,

who proved refractory to treatment and was evacuated to the Zone of the Interior, had originally been given a diagnosis and treated in Mexico three years prior to admission and had subsequently received several courses of therapy in the United States. Of those treated with emetine, carbarsone and Diodoquin, 1, or 0.57 per cent, continued to pass E. histolytica after one course of therapy, while 3, or 1.7 per cent, continued to have abdominal symptoms and, after two courses of therapy, were evacuated to the Zone of the Interior with a diagnosis of chronic colitis, manifested by persistent loose stools, abdominal discomfort, confirmatory sigmoidoscopic findings and repeatedly negative results of stool examinations for E. histolytica or pathogenic enteric organisms. Of those treated with emetine hydrochloride, carbarsone and chiniofon, none continued to pass E. histolytica after the initial course of therapy, but 1, or 2.7 per cent, experienced chronic colitis and was evacuated to the Zone of the Interior.

A second group of patients who must be considered in evaluating the results of therapy are those in whom symptoms again developed and who again began to pass E. histolytica in the feces within one month of their discharge from the hospital. It is impossible to determine whether these were patients who were reinfested following their discharge from the hospital or whether they had continued to harbor E. histolytica. We feel that the latter supposition is the more correct one, and it will be so considered in this report. Of those treated with emetine hydrochloride and two courses of carbarsone, 4, or 1.5 per cent, were in the second category, and of those treated with emetine hydrochloride, carbarsone and Diodoquin, 1, or 0.57 per cent, was readmitted.

Thus 9, or 3.9 per cent, of those treated with emetine and two courses of carbarsone, 5, or 2.8 per cent, of those treated with emetine hydrochloride, carbarsone and Diodoquin and 1, or 2.7 per cent of those treated with emetine hydrochloride, carbarsone and chiniofon (a total of 15, or 3.3 per cent of all patients) failed to respond satisfactorily to a single course of therapy. A total of 5, or 1.05 per cent, of the patients were evacuated to the Zone of the Interior, 1 being totally refractory to therapy and the other 4 because of the development of a chronic colitis. It is interesting to note that these 4 patients all had contributory psychogenic factors complicating the clinical picture.

Nineteen, or 4.1 per cent, of the patients, 17 of whom presented a severe clinical picture at the time of admission, continued to have loose stools with vague abdominal distress and slight erythema of the wall of the bowel with stools persistently negative for E. histolytica or for pathogenic enteric organisms after the completion of therapy. It was felt that the ulcerations and other damage caused by the previous action of the amebas had not had sufficient time to heal. These patients were given 8 Gm. of kaolin, 0.6 cc. of tincture of opium and 1 Gm. of

calcium gluconate twice daily for five days. Following this, the symptoms subsided entirely and the wall of the bowel appeared normal.

Using the previously outlined methods of treatment, reactions which were attributable to emetine hydrochloride were encountered in 27, or 5.7 per cent, of the patients. Precordial distress, mild in nature, occurring on the third or fourth day, developed in 15, or 3.2 per cent, of the patients. Increasing diarrhea, occurring on the third or fourth day, developed in 3, or 0.3 per cent of the patients. Three patients were treated for mitral stenosis. In 1 patient the murmur increased in intensity on the third day and the heart sounds of the second became faint on the fourth day, while no change was noted in the third patient during the entire period of emetine hydrochloride therapy. Sterile abscesses at the site of injection developed in 4, or 0.9 per cent, of the patients. Extrasystoles occurred in 1, or 0.2 per cent, of the patients, while neuritis developed in 2, or 0.4 per cent, of the patients. All the patients complained of local pain at the site of the injection; this pain persisted for three to four days after the injection. There were no patients who experienced any pronounced drop in blood pressure. No permanent residual effects were encountered.

Of those patients receiving chiniofon, 13, or 26 per cent, experienced moderate diarrhea and abdominal discomfort after three or four days' administration of the drug. For this reason, the routine use of chiniofon was discontinued.

Because of military limitations, it was possible to perform satisfactory follow-up examinations only on the members of the hospital personnel. Of the 166 members of the hospital staff treated, all except 3, or 1.7 per cent, have remained persistently free of the infection. These 3 were readmitted for a second course of therapy, following which they also have remained free of the infection.

Under the plan of therapy outlined in this article, the patients with acute amebiasis have had an average hospitalization of 20.6 days; the patients with chronic amebiasis, 24.6 days; the carriers, 18.4 days, and the patients with mixed infections, 24 days. One of the patients with hepatic abscess was hospitalized 57 days and the other 45 days. The average period of hospitalization for the entaire series was 20.9 days.

COMMENTS

An attempt has been made to present our experience in the diagnosis and treatment of amebiasis in the American armed forces in the Middle East. This disease is of importance not only to the military medical officer but to the civilian physician as well. American troops will return to the continental limits of the United States from many areas in which amebiasis is prevalent. Since the virulence of the organism is said to differ in various localities and since the disease in

any given endemic region affects the native population and the "foreigner" in a different manner, a report of the reactions of American troops to infection with E. histolytica should be compiled for each area in which the disease is prevalent.

We are in hearty agreement with the use of the term "amebiasis" rather than the term "amebic dysentery." The majority of the patients in this series had little or no diarrhea, nor did they have a dysenteric stool. The infection was, in general, a mild one. It is felt that the disease must be suspected in every one who has resided in an endemic area, particularly if there is a history of intermittent loose stools alternating with normal stools, mild intermittent abdominal pain, fatigability and vague psychosomatic complaints, among which are irritability, restlessness and gastrointestinal dysfunction.

SUMMARY

1. This report extends from November 1942 to November 1944, inclusive, and describes the experience of an American army hospital, located in the Middle East, with respect to 464 cases of amebiasis.

2. Monthly examinations of purged stools of the mess personnel of the hospital revealed that 36.4 per cent acquired infection with E. histolytica during the two year period.

3. Ninety per cent of the native workmen examined had one or more pathogenic organisms in their feces. Twenty-two per cent had E. histolytica.

4. At the time of admission, 26.5 per cent of the patients were asymptomatic; 35.7 per cent had mild symptoms; 24.4 per cent had moderate symptoms, and 13.4 per cent had severe symptoms.

5. Of the patients 41.8 per cent had no diarrhea at the time of admission; 33.8 per cent had loose stools, and 24.4 per cent had diarrhea.

6. Of the patients 57.5 per cent had abdominal pain; 40.2 per cent had abdominal tenderness; 15.6 per cent had an elevation of temperature and 11.9 per cent had an abnormally large number of leukocytes at the time of admission.

7. Of the patients with acute amebiasis 18.1 per cent had a dysenteric stool, and of the patients with chronic amebiasis, 16.7 per cent.

8. Of those examined sigmoidoscopically, 10.1 per cent of the patients with acute amebiasis, 10.2 per cent of the patients with chronic amebiasis and 75 per cent of the carriers had a normal-appearing wall of the bowel.

9. There was amebic involvement in 3.2 per cent of the appendectomies performed during the period covered by this report.

10. The average period of hospitalization was 20.9 days.

THROMBOANGIITIS OF PULMONARY VESSELS ASSOCIATED WITH ANEURYSM OF PULMONARY ARTERY

Report of a Case

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ANEURYSM of the pulmonary artery is a type of lesion encountered infrequently. Boyd and McGavack [1] reviewed the literature from 1833 to 1939 and reported 139 cases. Additional ones have been published by Hartwell and Tilden,[2] by Thompson [3] and by Breslin, Solway and Eisen.[4]

This paper reports a case in which an aneurysm of the right pulmonary artery of more than 10 cm. in diameter developed within a period of three months and was associated with thromboangiitis of both pulmonary arteries and veins.

REPORT OF CASE.

The patient, a white man 27 years old, was inducted into the United States Army in the spring of 1941 but was discharged two months later because of a perforated ear drum. During his short stay in the army he had two attacks of "influenza." On Jan. 11, 1942 he was treated at the Waterbury Hospital in Connecticut for an acute gonorrheal prostatitis.

On March 19, 1942 he was admitted to St. Mary's Hospital in Waterbury with severe pain in the left side of the chest and with a temperature varying from 100 to 104.6 F. A roentgenogram of the chest (fig. 1) showed a rounded area of increased density in the periphery of the left lung at the level of the third anterior interspace. It also disclosed a smaller lesion of fainter density about 1.5 cm. in diameter at the extreme base of the lung on the right side. A blood count revealed: red blood cells, 4,000,000; hemoglobin content, 78 per cent; white blood cells, 8,000, with polymorphonuclear leukocytes 68 per cent, small

From Undercliff, Meriden State Tuberculosis Sanatorium, and Central Laboratory of Pathology and Research, State of Connecticut Tuberculosis Commission.

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2. Hartwell, A. S., and Tilden, I. L.: Aneurysm of the Pulmonary Artery, Am. Heart J. **26**:692, 1943.

3. Thompson, S. A.: Differential Diagnosis by Means of Intravenous Contrast Medium of Two Cases Simulating Aneurysm of Pulmonary Artery, Am. J. Roentgenol. **46**:646, 1941.

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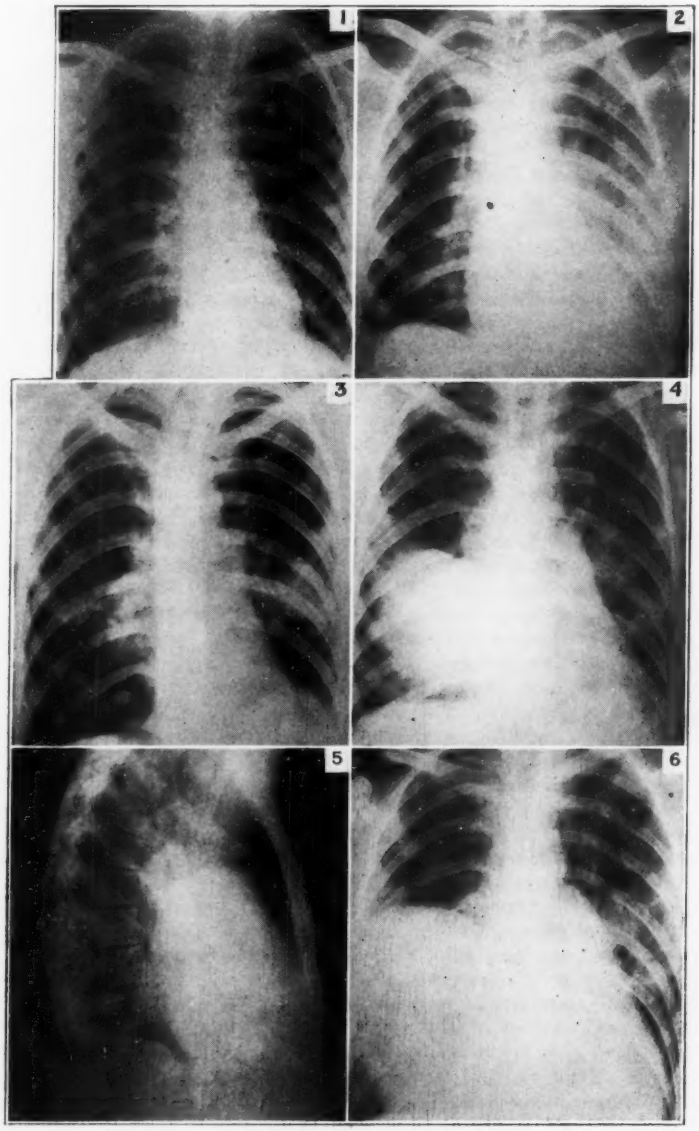


Figs. 1, 2, 3, 4, 5 and 6.—Roentgenograms of the chest. Figure 1 was taken on March 19, 1942; figure 2, on Nov. 27, 1943; figure 3, on Jan. 3, 1944; figure 4, on March 1, 1944; figure 5 (lateral view), on March 1, 1944, and figure 6, on April 21, 1944.

lymphocytes 10 per cent, monocytes 20 per cent and eosinophils 2 per cent. An agglutination test for typhoid H on March 28, 1942 elicited 3 plus reaction in dilution of 1:80, 2 plus in dilution of 1:160 and 1 plus in dilution of 1:320. This test was repeated on April 6 with the same results. No typhoid organisms, however, were recovered from either feces or urine. The patient's temperature remained elevated for two weeks, reaching 104.6 F. during the first four days and then gradually dropping to 100.6 F. by the end of fourteen days. Severe pain in the left side of the chest and in the legs and arms together with chills and a nonproductive cough persisted through the first two weeks. Reddened areas, macular in type, developed, first on the arms and legs and gradually spread over the body. For the first nine days the patient received sulfadiazine. His symptoms abated, although he still complained of occasional pain in the left side of the chest and of a cough. The roentgenograms were not repeated. The patient was discharged on April 15, 1942 with the impression that he had had typhoid.

Following his discharge the patient remained comparatively well, although he did have three or four attacks of "influenza."

He was readmitted to the Waterbury Hospital on Dec. 6, 1942 for a left epididymectomy. His temperature rose to 104.2 F., and he had severe chills during his postoperative course. He was given sulfanilamide, and by the end of four days his temperature was normal. The excised epididymis was reported to have shown round cell infiltration with no evidence of tuberculosis.

The patient contracted a "cold" about Nov. 1, 1943. In a few days this was followed by a sudden chill succeeded by a rise in temperature to 104 F. He also began to complain of severe and continuous pain in his entire chest. This was accompanied with a constant irritating cough. The sputum contained small amounts of blood. He was treated at home by a physician who diagnosed his disease as pneumonia of the left lung. During this period his temperature was from 103 F. to 104 F.

Because the patient showed no improvement, he was readmitted to St. Mary's Hospital on November 26. Examination on admission disclosed many rales in the lower lobe of the left lung, without evidence of consolidation. The results of urinalysis were normal. Examination of the blood showed 4,380,000 red blood cells, a hemoglobin content of 81 per cent and 16,100 white blood cells with polymorphocytes 88 per cent and lymphocytes 12 per cent. During the first four weeks of his hospitalization he was febrile, the number of white blood cells remained higher than normal, and there was a gradual decrease in the number of red blood cells, reaching a low of 3,550,000. Cultures of blood were sterile. Examination of the sputum for the bacilli of tuberculosis and for pneumococci gave negative results. The patient's temperature began to drop slowly beginning in the early part of December 1943. He was treated symptomatically and was also given a course of sulfadiazine. A roentgenogram of the chest on Nov. 27, 1943 (fig. 2) was interpreted as revealing pneumonia of the left lung with fluid in the left pleural cavity. A roentgenogram of the chest on Jan. 3, 1944 (fig. 3) revealed both a diaphragmatic pleurisy on the left side with the diaphragm about 5 cm. higher on the left than on the right side and an infiltration of the middle of the left pulmonary field. There was a small oval area of increased density at the base of the right lung with some denseness about the right hilus. The patient left the hospital against the advice of his physician on January 12.

On Feb. 26, 1944 he had hemoptysis with chills, fever and severe pain in the right side of the chest. He was readmitted to the Waterbury Hospital on March 1. On admission his temperature was 103.4 F., his pulse rate 120 and his respiration rate 30. Examination of the chest revealed moist rales, increased breath sounds

and decreased vocal and tactile fremitus over the right lung posteriorly from the angle of the scapula to the base. There was a friction rub on the right side anteriorly at the fourth interspace. The patient was immediately given sulfadiazine, with which he seemed to make slight progress. Shortly after the patient's admission cyanosis developed and he was put into an oxygen tent. He rebelled against this and was removed after twenty-four hours. He continued to complain of severe pain in the right side of the chest and of a constant irritating cough productive of blood-streaked sputum. His temperature remained elevated throughout his hospitalization.

A roentgenogram taken on admission (fig. 4) showed that the left side of the diaphragm was partially obscured. There was a dense area measuring 10 cm. in its greatest diameter below the third rib on the right anteriorly, confluent with the hilus and obscuring the right side of the heart. A lateral view (fig. 5) located the density in the anterior portion of the chest. A roentgenogram on March 9 disclosed an increase of this density. The impression was that he had pneumonia with encapsulated fluid in the lower anterior part of the right side of the chest. On examination of the blood, the red cell count was indicative of a moderate secondary anemia. There were 10,600 white cells with a normal differential count. The blood chemistry and urine were normal. The blood pressure was 132 systolic and 76 diastolic. Examinations of sputum for acid-fast bacilli were unsuccessful. Cultures of sputum and of blood were also negative for hemolytic streptococci and for pneumococci. The electrocardiogram was normal. On March 11, 1944 about 300 cc. of straw-colored, slightly bloody fluid was obtained from the right side of his chest, and this fluid was negative for acid-fast organisms. On April 7 the patient had a moderately severe hemoptysis. He was given two blood transfusions of 500 cc. each.

On April 20, 1944 the patient was transferred to the Undercliff Sanatorium in Meriden, Conn. His symptoms were as before. The temperature was 100 F., the pulse rate 112 and the respiration rate 30. Physical examination of the chest revealed normal breath sounds on the right side down to the third rib anteriorly. There were flatness and absence of breath sounds from the third rib anteriorly to the base of the lung. The breath sounds were well heard throughout posteriorly. Pulsation and murmurs were not noted. Hyperresonance with increased breath sound was found in the upper two thirds of the chest on the left side anteriorly. The lower third showed diminished breath sounds and impairment of the percussion note. Posteriorly, the conditions observed were normal. Heart sounds were regular, weak and rapid, but no murmurs were heard. The patient's condition continued to be critical. An attempt at thoracentesis on May 1, 1944 was unsuccessful, with only a small amount of pure blood being obtained. His sputum was persistently streaked with blood. The erythrocyte sedimentation rate was 62 per cent (31 per cent by the Cutler method). The urine was normal, and the Mazzini test elicited a negative reaction.

A stereoscopic roentgenologic examination of the chest on April 21, 1944 (fig. 6) revealed on the right side a mass occupying the lower half of the chest. The upper border was well defined, but the lower limits were less clearly outlined. This shadow extended to the base of the lung, except for a small area in the costophrenic angle. It seemed to extend beyond the spine in the midline. Above this area the lung appeared to be free of disease. On the left there was pronounced peaking of the diaphragm, with an area of increased but poorly defined density extending from the sixth to the eighth ribs posteriorly in all zones. This area was not as dense as that which was seen on the opposite side and appeared to be a faint haze rather than a definite density of the parenchyma.

On May 27, 1944 the patient died about five minutes after raising 240 cc. of blood.

Necropsy.—Gross Observations: The body was that of a well developed but extremely emaciated white man, 27 years old, measuring 167 cm. in length and weighing approximately 50 Kg. The skin was pale. Both pupils were round, and they measured 4 and 3 mm. for the left and right, respectively. Bloody foamy fluid exuded from the nares and the mouth. No enlarged lymph nodes were palpable in the supraclavicular and axillary fossae or in the groin. The finger tips were slightly cyanotic but not clubbed. Edema was absent. On the right the scrotum was of usual appearance. A small linear longitudinal scar was found over the left side of the scrotum. The left epididymis was absent. The left testicle, however, was similar to the right one. The abdominal organs occupied their usual position. No excess fluid was present in the abdominal cavity, and the peritoneum was intact.

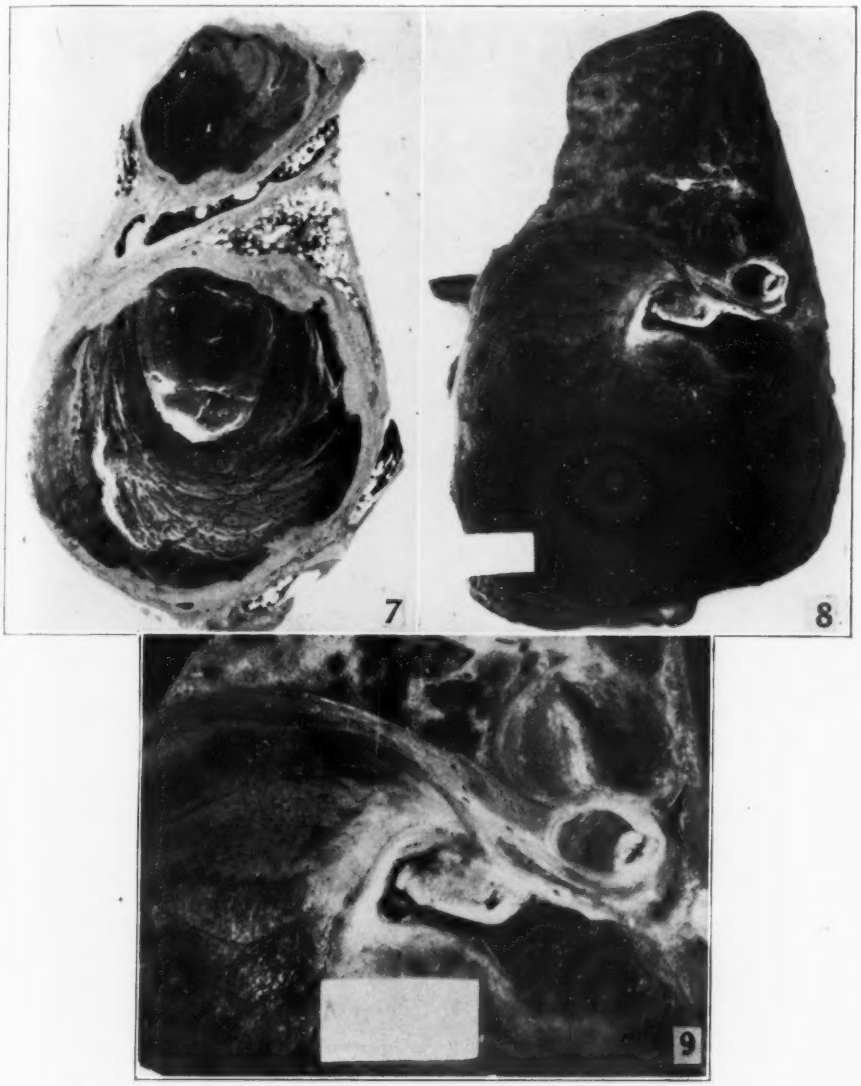
On removal of the chest plate, numerous fibrous adhesions were encountered, binding the anterior surface of the right lung to the chest plate. Only the upper part of the pleural space on the right side was patent. The pleural space on the left side was patent, with a few delicate fibrous adhesions extending between the visceral and the parietal pleura. The pericardial sac was partly covered by the left lung. The sac contained 30 cc. of a clear yellow fluid. Its lining was intact. The pulmonary artery contained fluid blood when it was incised at its origin.

Heart. The heart was the usual size and shape and weighed 270 Gm. The epicardium was intact. On incision, the musculature was a pale brownish color. The entire endocardium was smooth and glistening. The coronary ostia as well as the coronary arteries were patent. There was no evidence of hypertrophy or dilatation of either ventricle. The ductus arteriosus was obliterated. The aorta did not show any syphilitic lesions.

Lungs. The left lung, on removal, was largely air containing but slightly more resistant than is usual. The pleura revealed many small areas of dark red discoloration. The cut surface of the lower and upper lobes showed numerous lobules containing a hemorrhagic exudate. There were also several star-shaped areas of fibrosis in both the upper and the lower lobes. The largest one, measuring 6 by 8 mm., was found in the lateral segment of the lower lobe. No fresh infarcts were apparent on gross inspection. The left branch of the pulmonary artery, as seen on its cut surface near the hilus, was distended to a diameter of 2.5 cm. and contained a clot which was grayish red for about two thirds of its cut surface and dark red for the remaining third. Two bronchial lumens containing some clotted blood were found close to the posterior circumference of the vessel. The thrombus extended for about 2 cm. into the branch of the artery serving the upper lobe (fig. 7) but no thrombosed vessel could be found in the central or peripheral segments of the left lung.

The middle lobe of the right lung was displaced by a globelike structure with a firm capsule of grayish dark-purple color. It had dislocated the lower lobe posteriorly and laterally. On removal and incision, the lesion (fig. 8) measured 12 cm. in diameter and was largely occluded by a laminated clot of blood. Only a small tangential segment of the upper anterior lobe contained fluid blood. The part of the capsule adjacent to the hilus differed from the peripheral parts in its yellowish white color and in its firm structure. The compressed and atelectatic parenchyma of the middle lobe was found at the upper circumference of the lesion. Two large vessels (fig. 9) were located medially from its upper pole. The one situated cranially was rather thin-walled and measured 3 cm. in diameter. Two thirds of its lumen was occluded by a laminated purplish gray thrombus,

while the blood clot occupying the rest of the lumen seemed to be a postmortem formation. A bronchial lumen was noted at the upper circumference of this vessel. A second vessel was located between the large one just described and



Figs. 7, 8 and 9.—Figure 7 shows vessels from the hilus of the left lung (hematoxylin and eosin stain; × 2). Figure 8 shows the right lung. Figure 9 shows a close-up view of the right hilus and the upper pole of the aneurysm.

the wall of the globe-shaped aneurysm. The wall of this second vessel was grayish yellow and firm and measured 1 to 2 mm. in diameter. More than half of its lumen was occupied by an antemortem thrombus. Some compressed pulmonary parenchyma could be seen interposed between the vessel and the wall of the aneurysm. The cut surfaces of the upper and the lower lobe of the right lung showed numerous alveoli filled with aspirated blood. Small star-shaped areas of fibrosis were found in the upper lobe, but no changes in the vessels could be ascertained.

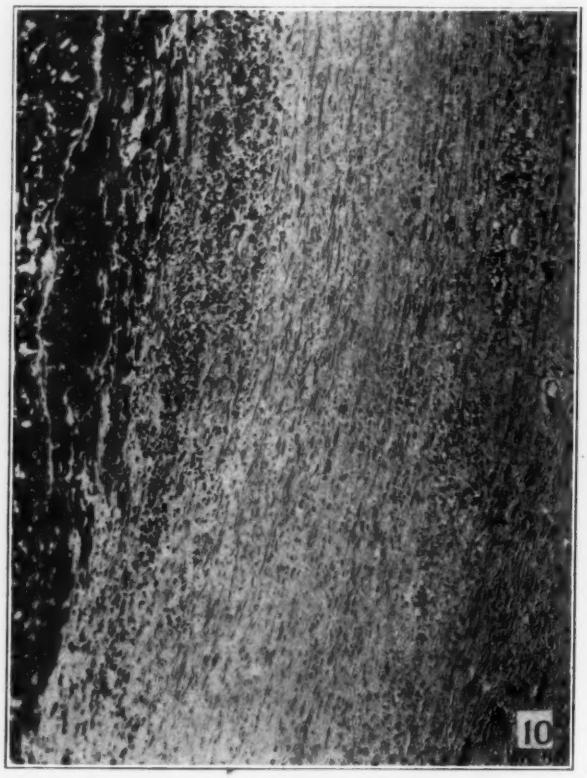


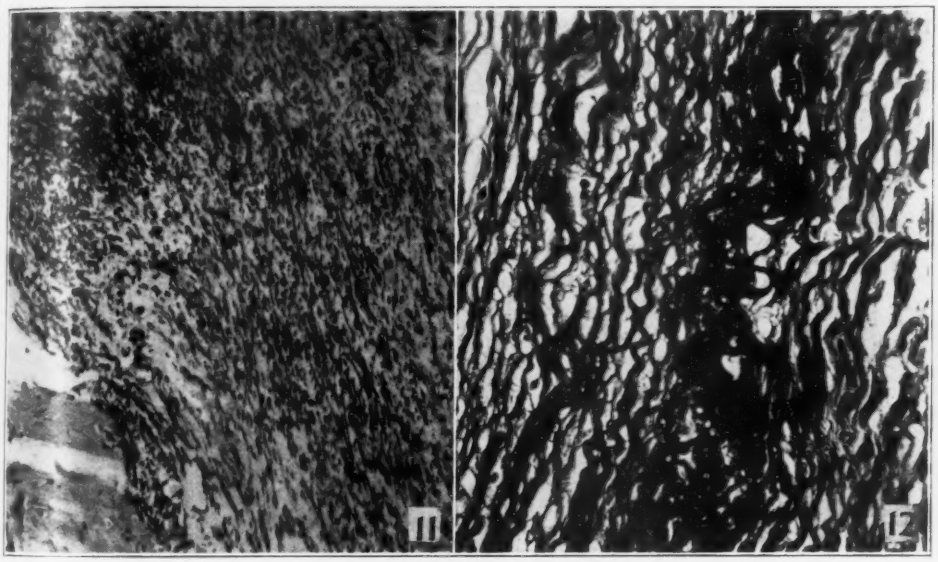
Fig. 10.—Wall of the right pulmonary artery (hematoxylin and eosin; × 100).

Study of the other organs failed to reveal any changes. There was no indication of passive congestion of the liver.

Microscopic Observations: Sections from the left lung revealed small fresh infarcts as well as organized ones in addition to numerous alveoli containing well preserved red blood cells. Several small arteries were occluded by organized and recanalized thrombi. Microscopic study of the large hilar vessels revealed that about half of the lumen of the pulmonary artery was occluded by an antemortem clot with organization starting at its periphery. The media was largely

replaced by fibrous connective tissue (fig. 7), and small round cell infiltration of varying intensity was seen throughout the wall. The internal elastic membrane could not be identified with a Van Gieson elastic tissue stain. Remnants of the outer elastic lamina were seen in various parts of the wall.

The changes in the large pulmonary vessels on the right side were similar to those on the left. The thin-walled cranially located lumen mentioned in the gross observation was identified as that of a pulmonary vein. The wall of the artery located between the vein and the aneurysm showed the media preserved for about two thirds of the circumference. In the remaining third, the media was replaced by fibrous tissue that was densely infiltrated by small round cells (fig. 10). At one point, vacuolated monocytes and round cells had entirely replaced the media.



Figs. 11 and 12.—Wall of the aneurysm. In figure 11 Masson's stain was used (× 80); in figure 12, Van Gieson's stain for elastic tissue (× 300).

The wall of the aneurysm was composed of bundles of fibrous connective tissue that were usually densely arranged. At some points, however, the connective tissue fibers were spread apart by monocytes, many of which showed a foamy cytoplasm. A few smooth, parallel muscle fibers could be identified close to the hilus (fig. 11), while fragments of wavy elastic fibers were seen (fig. 12) in sections of peripheral segments of the wall of the aneurysm.

COMMENT

Several features of this case are of particular interest. The development of a large aneurysm in a period of three months and without signs of murmurs or palpitation may be explained by assuming that the force

of the flow of blood, while sufficient to expand the damaged arterial wall, engendered such velocity that the physical signs usually associated with saccular aneurysm were not produced.

When the cause of the changes of the pulmonary vessels in this case is considered, rheumatic fever, Streptococcus viridans infection, syphilis and congenital malformation as reported by others [1] seem to be excluded by the clinical course and by the laboratory and necropsy observations.

The history of this patient reveals that he had contracted several infectious diseases. The first, gonorrhea, is unlikely to have furnished the etiologic agent. A gonococcic septicemia would most likely have produced a fulminating endocarditis with valvular involvement. The absence of the latter speaks against the assumption of a gonococcic septicemia. The second disease, diagnosed as typhoid, cannot in retrospect be considered as established, because the organisms were not recovered from the blood, urine or feces and the agglutinin titer did not rise on subsequent tests.

The pulmonary lesions found by roentgenologic examination during the first week of the patient's second illness are not characteristic of infarcts, and the occurrence of thrombophlebitis and subsequent embolism during the first week of typhoid would be unlikely. Unfortunately, this part of the patient's history became known only some time after death. It could not be ascertained whether the patient had been immunized against typhoid during his stay in the army.

It has been suggested that the conditions described herein may represent a variety of periarteritis nodosa. In 1942 there were pains in the extremities, a macular rash and patchy pulmonary infiltrations, compatible with a pulmonary form of periarteritis.[5] The fact that elevation of eosinophils in the blood was not present in this case does not necessarily exclude the possibility of periarteritis nodosa.[6]

The lesions of the smaller vessels might represent healed stages of periarteritis, although no local polymorphonuclear or eosinophilic infiltrations were observed in the recent lesions of the pulmonary vessel. Such observations were once made.[7] Should this case report be interpreted as an instance of the disease, the unusual involvement of the larger pulmonary vessels would add a new feature to the already complex syndrome of periarteritis.

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5. Elkeles, A., and Glynn, L. E.: Serial Röntgenograms of the Chest in Periarteritis Nodosa as an Aid to Diagnosis, Brit. J. Radiol. **17**:368, 1944.

6. Boyd, W.: Pathology of Internal Diseases, ed. 4, Philadelphia, Lea & Febiger, 1945, p. 96.

7. Eskelund, V.: Periarteritis nodosa der Pulmonalarterie und primäre Pulmonalsklerose, Acta path. et microbiol. Scandinav. **19**:13, 1943.

ACUTE PORPHYRIA

I. Investigations on the Pathology of the Porphyrins and Identification of the Excretion of Uroporphyrin I

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IT IS now well recognized that porphyria (so-called hematoporphyrinuria [Garrod,[1] 1923]) is a condition characterized by two main clinical types, the acute iodiopathic and the congenital, each possessing its characteristic symptomatology. In addition, there is recognized a toxic type due to various drugs, such as sulfonmethane, trinitrotoluene and sulfonamide compounds (Rimington and Hemmings,[2] 1939) which resembles clinically the acute idiopathic form. The classic case of congenital porphyria, studied in detail from the chemical and histochemical aspects by Fischer and his school and by Borst and Königsdörffer [3] (1929), was that of the man Petry. This work established a pathologic excretion of coproporphyrin in urine and feces, together with the appearance of pathologic porphyrin and uroporphyrin in the urine. These porphyrins were in the main type I porphyrin isomers, in contrast to the physiologically occurring type III protoporphyrin of the blood. Rimington [4] (1936) carried out a detailed examination of a similar condition in South African cattle, with similar observations, the large depositions of uroporphyrin I in the bones being striking, as in the case of Petry.

Investigations into acute porphyria, which is relatively common in Sweden, has more recently been undertaken by Waldenström [5] (1937). The main observation was the occurrence of coproporphyrin and uroporphyrin, both considered to be type III isomers. On this basis it was becoming accepted that an excretion of type I porphyrin was characteristic of the congenital form and an excretion of type III of the acute idiopathic form of the disease (Chandler, Harrison and Rimington,[6] 1939). In addition, there was no evidence of abnormal

From the Department of Pathology, St. Thomas's Hospital Medical School.

1. Garrod, A. E.: Inborn Errors of Metabolism, ed. 2, London, Oxford University Press, 1923.

2. Rimington, C., and Hemmings, A. W.: Biochem. J. **33**:960, 1939.

3. Borst, M., and Königsdörffer, H., Jr.: Untersuchungen über Porphyrie mit besonderer Berücksichtigung der Porphyria congenita, Leipzig, S. Hirzel, 1929.

4. Rimington, C.: Onderstepoort J. Vet. Sc. **7**:567, 1936.

5. Waldenström, J.: Acta med. Scandinav., 1937, supp. 82, pp. 1-254.

6. Chandler, F. C.; Harrison, G. A., and Rimington, C.: Brit. M. J. **2**:1173, 1939.

deposition of porphyrin in the tissues in the acute form, in contrast to observations in the congenital type. Recently there has appeared a study of the question by Watson and his colleagues (Grinstein, Schwartz and Watson,[7] 1945; Watson, Schwartz and Hawkinson,[8] 1945), in which it has been suggested that the uroporphyrin of acute porphyria, the porphyrin which is in fact the outstanding pathologic product in these diseases, is a mixture of uroporphyrin type I with a small amount of a type III compound isolated as a heptamethyl ester, and not an octamethyl ester, which is characteristic of uroporphyrin. Further contributions have been the finding for the first time of uroporphyrin in the liver and the feces.

Chandler, Harrison and Rimington[6] (1939) have pointed out that even today acute idiopathic porphyria is scarcely mentioned in the British literature. The present paper records the detailed investigation of another case which came to autopsy and brought to light a second case, an example of the "latent" form of the disease. The investigations reported in this paper were well advanced before the appearance of Watson's recent work mentioned previously, but this has stimulated their extension.

The remarks in the foregoing paragraphs give only a brief outline of the position. For extensive reviews the reader should consult publications by Mason, Courville and Ziskind[9] (1933), Vannotti[10] (1927), Watson[11] (1938), Dobriner and Rhoads[12] (1940), Turner[13] (1940), Nesbitt[14] (1944) and Welcker[15] (1945), in which a complete bibliography can be found.

REPORT OF A CASE

First Attack.—A girl aged 16, a domestic worker, complained of an attack of acute abdominal pain for six days, accompanied with vomiting and constipation. Her history revealed that she had been a premature baby with the remarkable birth weight of 14 ounces (397 Gm.), but after attaining 5 pounds (2.3 Kg.) at 4½ months she subsequently developed normally, apart from some kyphotic deformity, for which she received treatment, and rather subnormal intelligence. She had scarlet fever at the age of 8 years and a tonsillectomy at 11 years. Two

7. Grinstein, M.; Schwartz, S., and Watson, C. J.: J. Biol. Chem. **157**:323, 1945.

8. Watson, C. J.; Schwartz, S., and Hawkinson, V.: J. Biol. Chem. **157**: 345, 1945.

9. Mason, V. R.; Courville, C. B., and Ziskind, E.: Medicine **12**:355, 1933.

10. Vannotti, A.: Porphyrine und Porphyrinkrankheiten, Berlin, Julius Springer, 1937.

11. Watson, C. J., in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1938, vol. 4, p. 228.

12. Dobriner, K., and Rhoads, C. P.: Physiol. Rev. **20**:416, 1940.

13. Turner, W. J.: J. Lab. & Clin. Med **26**:323, 1940

14. Nesbitt, S.: Acute Porphyria, J. A. M. A. **124**:286 (Jan. 29) 1944.

15. Welcker, M. L.: New England J. Med. **232**:11, 1945.

months before being seen she had a generalized rash, diagnosed as psoriasis, and this had disappeared within a month. There was no history of photosensitivity or of recent ingestion of any drugs.

On admission, on May 6, the patient had been having convulsions for the previous four hours, and there were two epileptiform attacks, with incontinence, in the wards. The plantar responses were extensor. The temperature was 101.5 F. and the pulse rate 140. Lumbar puncture demonstrated nothing abnormal. The following day the patient was restless and uncooperative but complained of pain in the abdomen, mainly in the right iliac fossa. She said that it was burning in character and relieved by heat and raising the legs. Examination revealed a thin person with an external strabisums. She was menstruating. The temperature was 100.5 F. and the pulse rate 110. The tongue was furred but moist. There was tenderness on deep pressure in the right iliac fossa with guarding but no localized signs or hyperesthesia. Neither the liver nor the spleen was palpable. Catheterization gave a urine containing a trace of albumin, a few leukocytes and red blood cells and a moderate number of hyaline and granular casts. The blood pressure was 120 systolic and 80 diastolic.

Three days later the urine was noticed to darken on standing. The abdominal pain had slightly improved and ten days after admission had disappeared. She remained febrile with the temperature up to 99 F., for four weeks. Constipation was pronounced. A chart of the pulse rate is shown in figure 4. After six weeks she was discharged, symptom free.

Investigations.—On May 9 the urine contained a trace of albumin, a few leukocytes and red blood cells and a moderate number of granular and hyaline casts.

Spectroscopic examination revealed absorption bands at approximately 575 and 540 millimicrons, with a broad band extending to the right of 510 millimicrons due to a porphyrin-metal complex. Acidification to 1 per cent with hydrochloric acid produced the bands at 597 and 550 millimicrons of the acid porphyrin spectrum. The urine exhibited red fluorescence in ultraviolet rays. A diagnosis of acute porphyria was thus established.

On May 10 the leukocytes numbered 16,500, of which 74 per cent were polymorphonculear. The urine was found to contain large quantities of coproporphyrin and uroporphyrin. Details of the examination are given subsequently. The cerebrospinal fluid and plasma gave no fluorescence or spectroscopic evidence of the presence of porphyrin.

On May 15 a hematologic examination showed 5,620,000 red blood cells and a hemoglobin level of 100 per cent (Haldane).

On May 22 the blood urea level was 43 mg. per hundred cubic centimeters; plasma protein level 7.5 mg, and albumin level 3.4 mg. The icteric index was 5. The van den Bergh test elicited a negative reaction (direct). A hippuric acid synthesis test revealed 77 per cent normal function. The Schlesinger test elicited a 2 plus reaction for urobilin in the urine.

On May 23 a test for sensitivity to ultraviolet rays was carried out; an exposure of thirty seconds to an erythema dose produced no response. The patient then spent several days exposed to bright sunshine without effect.

On May 24 the number of leukocytes was 4,800; on May 30 the number was 6,100, and on June 6 it was 6,500.

Second Attack.—On December 7, the patient was again admitted to the hospital, complaining of abdominal pain and vomiting for five days. The pain was described as a continual dull ache in the umbilical region, relieved by heat. She was emotionally very unstable. The abdominal physical signs resembled

those previously noted, and the descending colon was loaded with feces. There was no oliguria. The temperature was 99.5 F. and the pulse rate 100. The pulse rate and temperature continued to rise throughout the subsequent course of the attack. The blood pressure was 150 systolic and 110 diastolic. The patient was very constipated.

On December 11 menstruation commenced, and the abdominal pain was increasing. On December 13 the patient became incontinent and catheterization was resorted to, but it was later abandoned because of the risk of infection. The incontinence varied in severity during the remainder of the attack. By December 15 there was some symptomatic improvement, but on December 21 an ascending paralysis commenced, being first manifested by loss of power in the limbs. Tendon reflexes disappeared, but there was no sensory disturbance The next day bronchopneumonia was evident, and on December 23 intercostal paralysis appeared. The patient died on December 25.

Investigations.—On December 22 a hematologic examination showed 26,000 leukocytes, with 87 per cent polymorphonuclear leukocytes, 5,000,000 red cells and a hemglobin level of 94 per cent (Haldane). The urine contained no albumin, but there was an occasional granular cast. The chemical examination of the blood showed: urea, 62 mg. per hundred cubic centimeters; plasma protein, 6.5 mg., and albumin, 3.2 mg. A slight increase of urobilin in the urine was found on only one occasion.

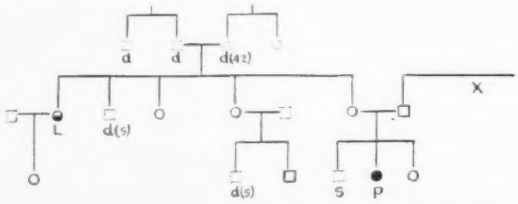


Fig. 1.—Relation of cases reported. (*d*, deceased at time of inquiry, age in brackets; *S*, stillborn; *L*, latent porphyrin; *P*, acute porphyrin; *X*, 16 relatives of patient's father examined with no abnormalities found. Dotted square and dotted circle indicate that urine was not examined.)

Treatment.—During the first attack the treatment was symptomatic. Belladonna produced no relief, the only effective drug being phenobarbital sodium. In the second attack supportive measures were instituted, but atropine and demerol (Pethidine [1-methyl-4-phenyl piperidine-4-carbonic acid]) were without effect. Again the minimal amount of pentobarbital sodium alternated with nepenthe was given. On December 11 1 Gm. of methionine was given daily and continued until December 21. On December 20 she was given Adexolin capsules (12,000 international units of vitiamin A and 2,000 units of vitamin D per cubic centimeter) and ascorbic acid.

Family History.—There was no history directly obtainable that any member of the family had suffered from porphyria. The patient's mother was said to be subject to "fits," but there was a coincidental history of hypertension. The maternal grandmother died at the age of 42, but the cause of death could not be elucidated. Morning specimens of urine from as many members of the family as possible were examined, with the results shown in figure 1. Of the persons examined, only 1, the patient's aunt, showed any evidence of latent

porphyria.[16] Of 27 members of the father's family included in three generations, the urine of 16 was examined and was normal.

Postmortem Examination.—The body was that of a well nourished girl of normal development. There was no hypertrichosis or pathologic pigmentation. The lips were deeply cyanosed.

Both lungs showed pneumonic consolidation in the lower lobes, particularly on the right. There were numerous small subpleural petechiae, and there was a small clear effusion in the right pleural cavity.

The heart weighed 9¼ ounces (262 Gm.) and appeared to have slight hypertrophy of the left ventricle. The pericardium contained a little clear fluid.

There was a small thymic remnant present. The intestinal tract appeared normal.

The liver weighed 40¾ ounces (1,155 Gm.) and had a well defined Reidel lobe. The capsule was thickened, and the cut surface showed a diffuse mottling, composed of pale areas, each approximately 2 by 2 mm. and pale gray. The color of the liver was considered remarkable, having a more definitely red appearance than normal. The spleen was about twice the normal size (weighing 5¾ ounces [162 Gm.]) and noticeably congested. The other abdominal organs appeared normal, except that the bladder contained 3 ounces (90 cc.) of pinkish urine. The uterus was of the infantile type. The brain (2½ pounds [1.1 Kg.]), spinal cord and peripheral nerves appeared normal to the naked eye. There was no apparent abnormality of the marrow removed from the upper part of the right femur and no macroscopic evidence of deposition of porphyrin in the bone.

Microscopic examination of the section of the organs stained with hematoxylin and eosin revealed no striking abnormalities, with the following exceptions: The liver showed slight thickening of Glisson's capsule, with a small degree of small round cell infiltration into it and the neighborhood of the portal areas. In the latter areas there was some fatty degeneration of the liver cells, also shown in frozen sections. The sinusoids showed some engorgement. In the center of many lobules were areas of liver cells in early stages of necrosis. This varied from cloudy swelling to swollen cells with coarsely granular cytoplasm and pyknotic nuclei. There was no infiltration of inflammatory cells into these zones, and the Kupffer cells were inconspicuous. Many of the liver cells showed deposits of granular pigment (fig. 6 *A*). These were to be found in the necrotic areas and also scattered through the liver substance. There were very few Kupffer cells containing these granules. The pigments appeared to be of two types: the first, golden yellow, large and small granules, and the second, small orange-red granules or diffuse patches of pigment throughout a portion of the cell. Sections stained for iron showed little indeed of this material to be present.

The kidneys showed some congestion of the glomerular capillaries, with swelling of the endothelial cells lining Bowman's capsule. In the tubules, particularly the convoluted tubules, were found pronounced degenerative changes with casts of epithelial debris. There appeared to be no pigment granules identifiable in the cells.

Sections of the central nervous system revealed no gross abnormalities, and some degree of postmortem change made the identification of minor degeneration difficult.

16. The urine reacted weakly with paradimethylaminobenzaldehyde to give a red product insoluble in chloroform and with absorption bands at 570 to 555 and 525 millimicrons. The latter was extremely faint. The coproporphyrin content of the urine was estimated to be only 12.5 micrograms per liter, and no uroporphyrin could be detected.

Ultraviolet Microscopic Examination.—Liver: Among the cells laden with pigment granules previously described were clumps of pigment exhibiting a bright brownish red fluorescence. There were numerous areas of this type. The emission spectrum showed an intense bright band from 620 to 660 millimicrons. The brightest portion of the spectrum was in the neighborhood of 620 millimicrons.

Kidney: The tubules were lined with a ring of red fluorescence, which seemed most pronounced in the collecting tubules. There was also a diffuse reddish fluorescence among the necrotic epithelial elements contained in the tubules. The emission spectrum was continuous from 620 to 650 millimicrons, the brightest portion being at 620 millimicrons.

Costal Cartilage: Macroscopically there was present a red fluorescence in the central portion of the cut surface. Microscopically this appeared as a ring of red fluorescence immediately around the cartilage cells or alternately as small circumscribed globular zones of fluorescence adjacent to the cells. The emission spectrum ranged from 610 to 650 millimicrons, being brightest at 63 millimicrons.

The spinal cord, cerebellar cortex, cerebral cortex and pituitary gland, all showed minute pinkish orange fluorescent "droplets" scattered throughout the tissue. In the pituitary gland the effect was most noticeable in the posterior portion. There was insufficient fluorescence in any of these sections to identify the emission spectrum. Further work is in progress on the nature of this fluorescence.

The Excretion of Porphyrin.—Urine: The excretion of porphyrin in the urine was measured by the method of Rimington[17] (1943) a Hilger fluorometer with Chance No. 3 orange filter in the secondary beam being used. A solution of coproporphyrin, 0.5 microgram per cubic centimeter in 0.25 per cent hydrochloric acid, was used as a reference standard. The calibration curve (fig. 2) was almost identical with that of Rimington[17a] (1943), a different instrument being used. In the determination of total porphyrin by adsorption onto kieselguhr it was found impossible to remove all the residual blue fluorescence even when acetic acid washings were employed as advised by Rimington. This gave rise to the greatest trouble with low concentrations of uroporphyrin.

Feces: The fecal coproporphyrin was estimated in the earlier specimens by grinding 5 to 10 Gm. of wet feces with sufficient anhydrous sodium sulfate to bring the mixture to a dry powder. The powder was then moistened with about 3 cc. of glacial acetic acid and extracted with ether for three hours in a Soxhlet apparatus, when no more coproporphyrin was extracted. The ether extract was washed three times with water or 10 per cent sodium chloride if emulsions were difficult. Extraction of ether was carried out with 1 per cent hydrochloric acid until no more porphyrin was removed (fluoroscopic examination). The porphyrin was taken back to ether after the addition of solid sodium acetate and thence returned to 0.25 per cent hydrochloric acid. The last extract was washed with chloroform which removed a small amount of porphyrin. If the remaining hydrochloric acid extract was pigmented, it was taken back to ether and extracted again with 0.25 per cent hydrochloric acid. The final extract was made up to 50 cc. with 0.25 per cent hydrochloric acid and read in the fluorometer.

During the analysis of the feces obtained at necropsy, it was found that this method did not effect a complete extraction of the fecal coproporphyrin.

17. (*a*) Rimington, C., and Schuster, E.: Biochem. **37**:137, 1943. (*b*) Rimington, C.: ibid. **37**:443, 1943.

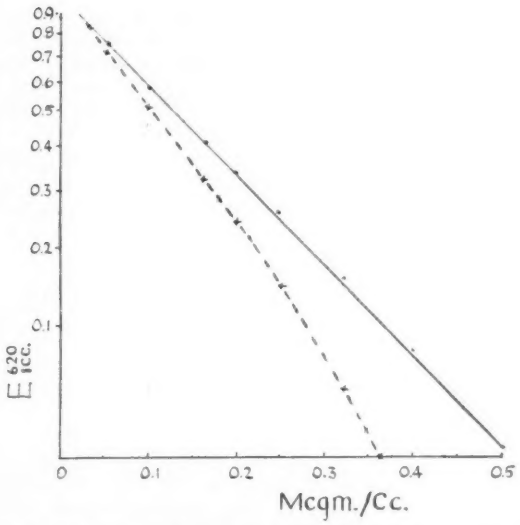


Fig. 2.—Calibration curve of porphyrin with Hilger fluorometer. (— — —copro-porphyrin in 0.25 per cent hydrochloric acid; x - - - x—uroporphyrin in normal tenth sodium hydroxide.)

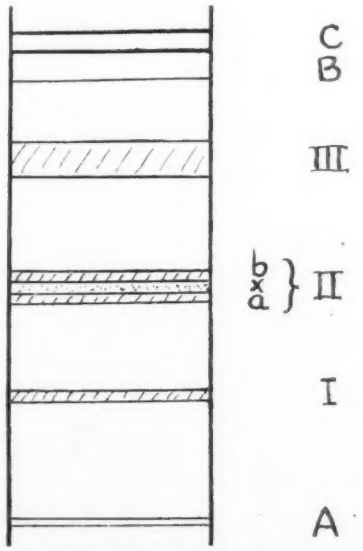


Fig. 3.—Composite diagram of the developed chromatogram of fecal extract. (Figures in brackets indicate ratio of chloroform: light liquid petrolatum in the solvent required for elution. *A*, yellow pigment [1:10]; *I*, protoporyphyrin [1:5]; *II*, porphyrin [1:4]; *III*, uroporphyrin [1:1]; *B*, yellowish green pigment; *C*, brown pigment.)

The residue from the extractions by the Soxhlet apparatus was treated with methyl alcohol, saturated with hydrochloric acid according to the technic of Schwartz and Watson[18] (1941). The extract was transferred to chloroform and adsorbed on an aluminum oxide column (Savory and Moore) from a mixture of 1 volume of chloroform and 10 volumes of light liquid petrolatum. Four porphyrin bands were developed under ultraviolet rays (fig. 3).

Another chromatogram of zone II was made on a new column, and bands *a* and *b* were obtained with better separation and free from the greenish pigment.[19] The solvent was evaporated off and the residue reesterified with methyl alcohol and hydrochloric acid. The absorption spectrums in chloroform were:

(*a*) 622; 580-562; 534; 499 millimicrons [18]
(*b*) 623; 582-566; 535; 500 millimicrons

The spectrum of *a* matched that of a pure coproporphyrin methyl ester. The dry coproporphyrin ester was saponified with 0.5 cc. of 25 per cent hydrochloric acid and the concentration diluted to 0.25 per cent and the porphyrin estimated fluorometrically (table 2).

The uroporphyrin (zone III) eluate was evaporated to dryness and neutralized with 10 per cent sodium hydroxide solution and diluted to 25 cc. with tenth-

TABEL 1.—*Corrections of Volumes of Urine for Incontinence*

Date, December	Urine Collected (Cc.)	Total Creatinine Obtained (Gm.)	Corrected Volume of 24 Hour Output (Cc.)
9	560 *	0.861	560
10	420 *	0.858	420
11	294	0.467	475
12	585 †	0.390	1,130
13	635 *	0.750	635
15	450 *	0.744	450
17	520	0.658	600
19	210	0.276	570
20	164	0.206	595
22	305	0.436	525

* A complete twenty-four hour collection.
† This specimen was contaminated with an unproductive saline enema. The patient was incontinent during this period.

normal sodium hydroxide solution. An aliquot diluted with tenth-normal sodium hydroxide solution was used for the fluorometric estimation of the uroporphyrin.

Porphobilinogen in the urine was estimated immediately at the termination of a twenty-four hour collection by the method of Waldenström and Vahlquist[20] (1939) a Hilger absorptiometer being used and 1 unit of porphobilinogen per cubic centimeter of solution being given by E 550 1 CM = 0.545, an Ilford 605 filter being used (maximum absorption at 550 millimicrons).

Corrections for Loss of Urine During Periods of Incontinence.—In order to assess the daily output of porphyrin and porphobilinogen during periods of incontinence the creatinine content of the specimens obtained during the twenty-

18. Schwartz, S., and Watson, C. J.: Proc. Soc. Exper. Biol. & Med. **47**: 390, 1941.

19. The fluorometric estimation of this fraction as "coproporphyrin" indicated 1,050 micrograms per hundred grams of wet feces (table 2).

20. Waldenström, J., and Vahlquist, B.: Ztschr. f. physiol. Chem. **259**: 213, 1939.

four hours was estimated, and the appropriate correction applied, assuming a 100 per cent collection to contain 0.75 Gm. of creatinine per twenty-four hours. Table 1 indicates these corrections.

Figure 4 shows the excretion of porphyrin and porphobilinogen in the urine during the first and second attacks respectively. Table 2 gives the excretion of porphyrin in the feces.

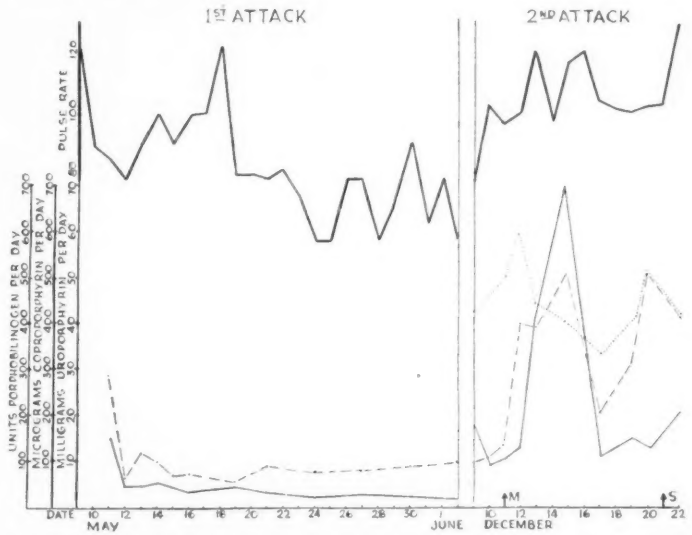


Fig. 4.—Coproporphyrin, uroporphyrin and porphobilinogen. (—.—. coproporphyrin micrograms per day; ——— uroporphyrin mg. per day; ..... porphobilinogen units per day; ——— midnight pulse rate; *M*,—methionine therapy commenced. *S*.—methionine therapy stopped).

TABE 2.—*Fecal Excretion of Porphyrin*

Date	Total, Gm.	Coproporphyrin by Ether Extraction, Micrograms per 100 Gm.	Additional Coproporphyrin by Absorption, Micrograms per 100 Gm.	Total Coproporphyrin, Micrograms per 100 Gm.	Uroporphyrin, Micrograms per 100 Gm.
5/22-5/24.....	225	38	...	....	....
5/25-5/27.....	271	7.7	...	....	....
5/28-5/30.....	267	25.5	...	....	....
5/31-6/1.....	110	23.7	...	....	....
12/11.....	...	344	...	....	....
12/18.....	...	87.5	...	....	....
Port mortem.....	...	470	860	1.33	2.82

THE ISOLATION AND IDENTIFICATION OF THE PORPHYRINS

Urine.—During the first attack a sample of the urine was examined by Professor Rimington, who found an easily isolated uroporphyrin, the melting point of the ester being 253 to 255 C. The coproporphyrin was present only in a small amount, and he managed to obtain with

difficulty both coproporphyrin III and coproporphyrin I methyl ester in the approximate ratio of 2:1. The melting point of the former was 178 C.

During the second attack I examined 1,500 cc. of dark port wine-colored urine. Spectroscopically the bulk of the porphyrin appeared to be present as the metal complex. The urine was acidified with 75 cc. of glacial acetic acid and extracted with 500 cc. of ether. Forty cubic centimeters of light liquid petrolatum was added to facilitate the breaking down of the emulsion. After prolonged standing the remaining emulsion was spun off, leaving a brownish residue at the bottom of the tubes. The aqueous material, still exhibiting a weak metal complex spectrum, was again extracted with 500 cc. of ether, and the ether extracts combined. The emulsion was again spun down and the residue was washed with ether. The former was combined with the first residue and the latter returned to the combined ether extracts.

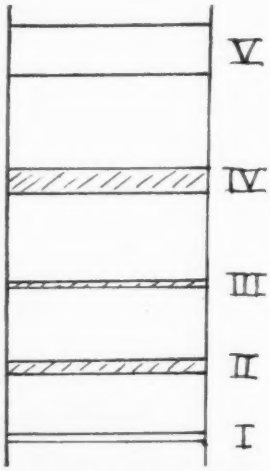


Fig. 5.—Composite diagram of the developed chromatogram of the liver extract. (Figures in brackets indicate ratio of chloroform and light liquid petrolatum in solvent required for elution. *I*, yellow pigment [1:10]; *II*, protoporphyrin [1:17]; *III*, porphyrin? [1:15]; *IV*, uroporphyrin [1:1]; *V*, greenish brown pigment.

Isolation of the Coproporphyrin: The combined ether extracts were prepared in the usual way, thrice washed with water and six times extracted with 1 per cent hydrochloric acid. At this stage no more porphyrin was extracted into the hydrochloric acid, but the ether still contained porphyrin. The ether was allowed to stand overnight over 1 per cent hydrochloric acid when all the porphyrin was finally extracted with five portions of 5 per cent hydrochloric acid.

After addition of sodium acetate to the combined hydrochloric extracts the porphyrin was transferred to ether, taken back to 0.25 per cent hydrochloric acid and thence back to ether. Most of the extraneous pigment had thus been removed. After removal of the ether the dry residue was esterified with methyl alcohol saturated with dry hydrochloric acid. The product crystallized from

chloroform–methyl alcohol was recrystallized four times from these solvents, being finally obtained as pale feathery crystals (fig. 6 *B*). The melting point[21] of the product was 236 to 241 C., indicating that it was mainly type I porphyrin.

Isolation of Waldenström's uroporphyrin: The precipitated residue from the ether extraction was first prepared. It was dissolved in 3 per cent solution of ammonia, and the precipitated phosphate was spun down. The spectrum of the ammonia solution exhibited four bands: 610, 570, 530 and 500 (extinction) millimicrons. The solution was acidified to p_H 4 with hydrochloric acid and allowed to stand overnight in the refrigerator. The precipitate was spun off, twice washed with 2 per cent acetic acid and dried over sulfuric acid. The residue was then treated with methyl alcohol and hydrochloric acid overnight and filtered on sintered glass from a small black residue. On admixture with chloroform and water a heavy black precipitate came down. This was separated by filtration and centrifugation and proved to be insoluble in hot chloroform, ammonia and 50 per cent hydrochloric acid. It was dissolved in 2 per cent acetic acid and exhibited a broad band from 505 to 495 millimicrons. Treated according to Schlesinger's technic it exhibited a dark green fluorescence. It was considered to be mainly porphobilin.

The chloroform solution was concentrated, and impure porphyrin ester crystals were obtained after the addition of methyl alcohol. One hundred and sixty milligrams of such material was obtained. This product was thrice recrystallized from chloroform and methyl alcohol, typical crystals of uroporphyrin III methyl ester being obtained (melting point 260 to 262 C.). The yield was 50 mg. Fractionation of the mother liquors yielded an additional 7 mg. of ester (melting point, 254 to 259 C.).

The Residual Porphyrin of the Aqueous Layer: The liquid residue after extraction with ether and separation of the solid deposit showed a weak spectrum of the metal complex. After preliminary experiments with other samples of urine, the following technic was adopted. The acid liquid was subjected to chromatography on a 20 cm. column of aluminum oxide. A light yellow band at the bottom of the column underwent elution while the last of the liquid was passing through the column. After adsorption was complete, the elution was begun with 750 cc. of 50 per cent (by volume) acetic acid. The first 400 cc. of eluate contained a strong solution of porphobilin giving a dark green fluorescence with Schlesinger's test. This eluate contained only traces of porphyrin. The passage of an additional 200 cc. of acetic acid brought out a considerable quantity of a mixture of free porphyrin and metal complex (spectrum 595, 578 and 540 millimicrons). Two hundred cubic centimeters of glacial acetic acid eluted a small quantity of metal complex. Finally elution with 150 cc. of 7 per cent ammonia brought out all the remaining pigment with most of the porphyrin.

This eluate was combined with the acetic acid eluate and brought to p_H 4. No porphyrin could be induced to precipitate during a fortnight. The liquid was therefore again passed through an aluminum oxide column at p_H 4, and the column was washed with 200 cc. of water, which eluted a small amount of porphyrin. The eluate was therefore adjusted to p_H 3.4 and again passed through the column, which was then washed with 250 cc. of water, no porphyrin then being removed. The porphyrin was completely eluted with 150 cc. of 10 per cent ammonia. The eluate was adjusted to p_H 4 with concentrated hydrochloric acid, when the porphyrin quantitatively precipitated out as pale brown

21. This and all subsequent figures for melting points are corrected and determined by the micro method.

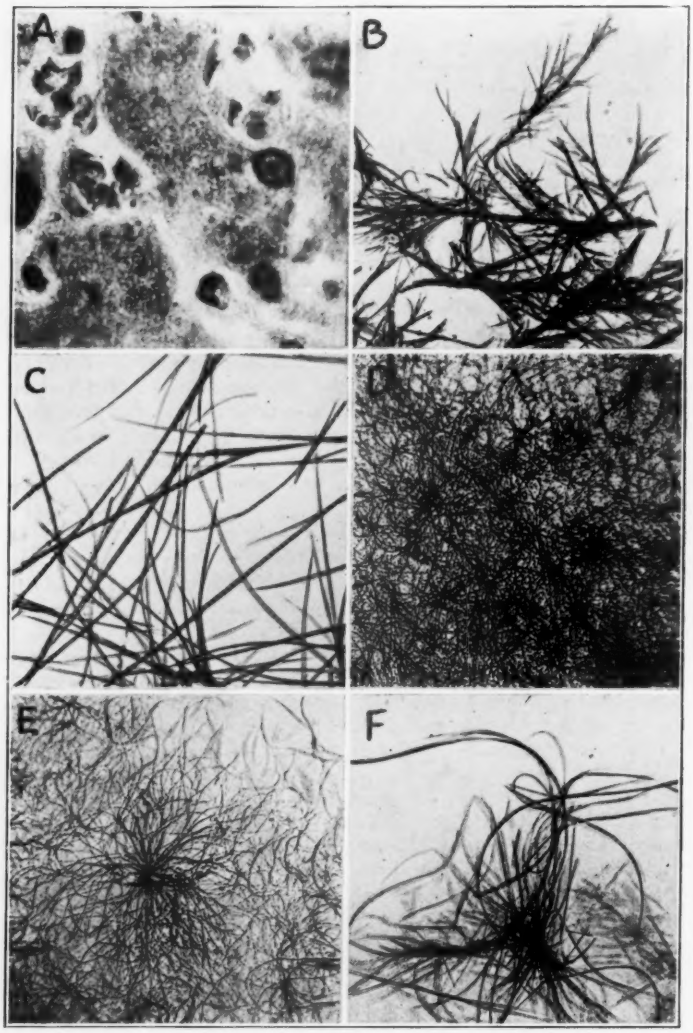
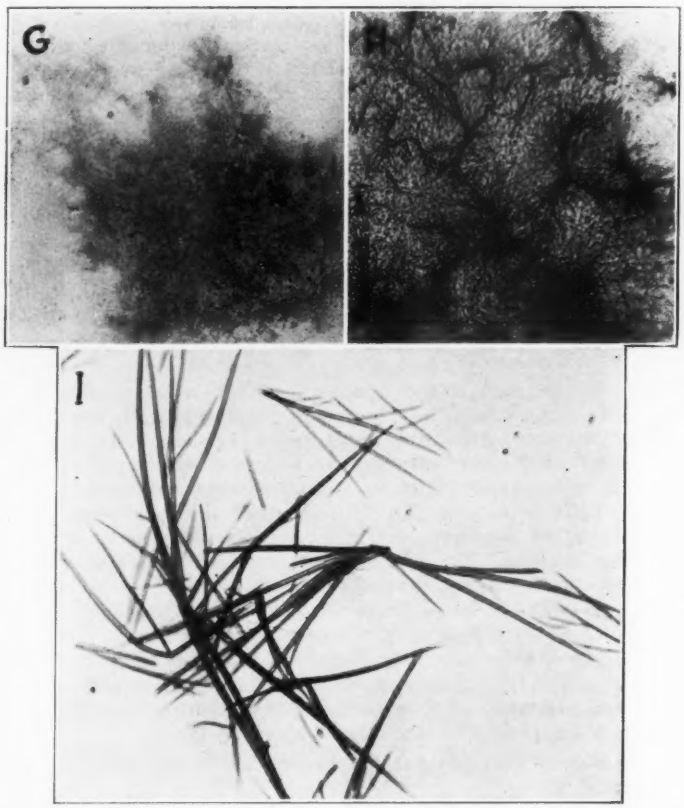


Fig. 6.—*A*, liver. Zone containing yellow and orange-red pigment granules (× 700); *B*, crystals of coproporphyrin I ester isolated from urine (the magnification in this and subsequent figures is × 350). *C*, crystals of coproporphyrin I ester isolated from feces; *D*, crystals of uroporphyrin I ester isolated from feces; *E*, crystals of uroporphyrin I ester isolated from liver; *F*, crystals of uroporphyrin

(Legend continued on next page)

floccules. The precipitate was spun off, washed with 4 cc. of water, dried over sulfuric acid and esterified. After one recrystallization the melting point was 256 to 259 C. The yield was approximately 4 mg. A total yield of 61 mg. of Waldenström's uroporphyrin III methyl ester was therefore obtained from the 1,500 cc. sample of urine.

Feces.—Fifty grams of feces, obtained post mortem was partially dried and extracted by grinding with methyl alcohol and hydrochloric acid by the method of Schwartz and Watson[18] (1941). This process occupied two days. The



isolated from urine (after second esterification); *G*, material obtained from the "red-brown zone" on chromatography of the uroporphyrin isolated from the urine; *H*, the same material as that which is shown in *G*, after reesterification; *I*, crystals of coproporphyrin I ester obtained by decarboxylation of uroporphyrin isolated from urine.

esters were transferred to chloroform and washed with 7 per cent ammonia and 10 per cent sodium chloride, dried over anhydrous sodium sulfate and filtered. The volume of the chloroform was reduced to 48 cc. and 10 volumes of light liquid petrolatum added. After filtration of the precipitated material the

esters were adsorbed on an aluminum oxide column. The column was then treated with mixtures of chloroform and light liquid petrolatum of increasing chloroform content, each mixture first being used to extract the precipitate before passage through the column. Three zones of porphyrin developed.

Another chromatogram was made of zone I and gave but a single porphyrin band, which was eluted with chloroform and light liquid petrolatum (1:6). The solution contained a moderate quantity of protoporphyrin but was not further examined.

Zone II according to the second chromatogram developed two porphyrin bands. The lower band was eluted with chloroform and light liquid petrolatum (1:3.4) and on four recrystallizations yielded an unweighable quantity of coproporphyrin I methyl ester with a melting point of 250 to 252 C. (fig. 6*C*). Crystals obtained from the mother liquor melted at 240 to 247 C. and were, therefore, mainly coproporphyrin I. The upper band, about equal in density in ultraviolet rays to that due to coproporphyrin, was eluted with chloroform and light liquid petrolatum (1:3), which also brought out some brownish pigment. This material could not be induced to crystallize. The bands in chloroform were 623, 582 to 564, 534 and 499 millimicrons.

Zone III was readsorbed on aluminum oxide from chloroform and light liquid petrolatum (1:6) and only a single porphyrin band could be developed. This was eluted with chloroform and light liquid petrolatum (1:1.4). Three crystallizations yielded 1.2 mg. of uroporphyrin ester with a melting point of 274 to 277 C. (fig. 6*D*). Absorption bands in chloroform were 628, 588 to 565, 536 and 500 millimicrons.

Liver.—Fifteen grams of liver was extracted by the same technic as that used for the fecal extraction. No coproporphyrin could be identified with certainty in the ether extract, but a small amount of protoporphyrin was present. The residue from the ether extraction was extracted with methyl alcohol and hydrochloric acid and adsorbed on a column of aluminum oxide from chloroform and light liquid petrolatum (fig. 5). The 1:7 eluate contained traces of protoporphyrin, and 1:5 eluate brought out a further trace of porphyrin, which could not be identified. The 1:1 chloroform and light liquid petrolatum eluate removed an intense porphyrin band. The bands of the ester in chloroform were 627, 58 to 568, 535 and 501 millimicrons. An aliquot of the chloroform solution was used for fluorometric assay after saponification. This gave 0.61 mg. per hundred grams of wet weight tissue, i. e., 7 mg. in the entire liver.

Crystallization of the ester from the remainder of the chloroform solution yielded, after recrystallization, approximately 100 micrograms of uroporphyrin I ester, with a melting point of 282 to 285 C. (fig. 6*E*).

Examination of Other Tissues for the Presence of Porphyrin.—The spleen, marrow and brain were analyzed by the same technic as that employed in the case of the liver. The only porphyrin identified was a trace of presumed protoporphyrin in each tissue.

Further Experiments on the Nature of the Uroporphyrin in the Urine.—Five milligrams of the uroporphyrin ester (melting point of 262 C.) was adsorbed onto precipitated calcium carbonate B. P. from benzene and light liquid petrolatum (3:1) (Grinstein, Schwartz and Watson,[7] 1945). Only two porphyrin bands developed. The lower was eluted with benzene and chloroform (5:1). On a second chromatogram it was an entity. The melting point of the ester was 260 to 261 C., and after reesterification and recrystallization it was 265 C. (fig. 6*F*). The free porphyrin was soluble in ethyl acetate from aqueous solution at p_H 3.5.

The upper band was red-brown, as described by Grinstein, Schwartz and Watson[7] (1945), and could be eluted with chloroform only after addition of ⅛ volume of acetic acid. The eluate, after being washed with ammonia, yielded ill defined crystals with a melting point of 270 to 305 C. (fig. 6 *G*); the bands in chloroform (624, 570, 532 and 502 millimicrons [IV, III, II, I]) were not suggestive of the presence of much metal complex. Reesterification of this material gave a product with a melting point of 262 C. and of crystal form similar to that of material obtained from the lower band (fig. 6 *H*).

If the uroporphyrin ester, with a melting point of 262 C., isolated from the urine is reesterified before adsorption on calcium carbonate, adsorption on this material leads in the main to the development of a single band, only a minute amount of the "red-brown" zone at the top of the column being apparent.

Decarboxylations.—The uroporphyrin isolated from the urine (a melting point of 260 to 262 C.) and the reesterified material from the lower zone of the calcium carbonate chromatogram (a melting point of 265 C.) were subjected to decarboxylation. The ester was heated for three hours at 180 to 185 C. in 1 per cent hydrochloric acid. After cooling and the addition of sodium acetate the solution was extracted with ether and the ether washed with water to remove acetic acid and evaporated to dryness. The solid material was then esterified.

Uroporphyrin in the Urine.—Seven and five-tenths milligrams were decarboxylated, and the melting point obtained was 208 to 215 C. A chromatogram of this product was then made on calcium carbonate, being adsorbed from a mixture of equal parts of benzene and purified benzine (petroleum ether) and developed with benzene and chloroform (20:1). Three bands developed. At the top of the column was a small "red-brown" zone containing porphyrin. Next was a porphyrin band 1 cm. wide, immediately below which there was a distinct band 0.5 mm. in width, but this could not be separated from the main band and was eluted with it (*a*). The passage of chloroform through the column led to the development of a porphyrin band 1 mm. wide (*b*), which was eluted with chloroform. Crystallization of this product gave small rosettes of needles (melting point of 196 to 206 C.). Crystallization of the main product (*a*) yielded an ester with a melting point of 216 to 225 C. This was subjected to a second decarboxylation (as advocated by Grinstein, Schwartz and Watson[7] and Watson, Schwartz and Hawkinson[8] [1945]) and yielded an ester with a melting point of 215 to 225 and a yield of 3.4 mg. (44 per cent of starting material). The second decarboxylation had produced no appreciable change. Recrystallizing this product four times gave an ester with a melting point of 236 to 245 C., which was considered to be nearly pure coproporphyrin I methyl ester crystals (similar to fig. 6 *I*).

Chromatographed Uroporphyrin.—The whole of this material was decarboxylated. The melting point of the ester directly obtained was 207 to 215 C. After four recrystallizations nearly pure coproporphyrin I methyl ester was obtained (melting point, 238 to 245 C.) (fig. 6 *I*).

COMMENT

The clinical features of the case reported are classically those of acute idiopathic porphyria and require but little comment. From the therapeutic standpoint it is difficult to control the abdominal pain which is due to violent gastrointestinal spasm, severe contraction of

the stomach having been observed by Chandler, Harrison and Rimington[6] (1939). (See also Vannotti[10] [1937].) Fortunately, in the present case laparotomy was avoided. It is, however, remarkable how little effect antispasmodic drugs appear to have on this symptom. The mode of death in this patient was also classic, ascending paralysis being basically responsible.

The second case, discovered in the routine examination of the patient's relatives, was of the "latent type" of Waldenström. No history of symptoms ascribable to porphyria was noted, and there was no pathologic excretion of porphyrin. The familial incidence would be in agreement with Waldenström's[5] (1937) view that the condition is a dominant one, but it would appear from the present and the published data that the gene carries a low incidence of expression.

Quantitative studies of the excretion of porphyrin in acute porphyria are scanty, largely owing to the specialized methods required for their elucidation. Excretions of up to 50 mg. of uroporphyrin daily in the urine have been noted (measurements cited by Dobriner and Rhoads,[12] 1940). With the advent of a fairly rapid micro method devised by Rimington[17] (1943) it has now become possible to make such studies with frequent examinations of specimens. The only case in which this has so far been done appears to be that followed by Rimington himself, and the urinary excretion of uroporphyrin fluctuated wildly, even during the subsidence of symptoms. He also noted a general correlation between the pulse rate and the amount of porphyrin excreted. The present data are in general agreement with his observations but do not show such variation, with the exception of the peak in the excretion of coproporphyrin and uroporphyrin on December 15 (fig. 4). At this time there was some improvement in the abdominal pain, the maximum intensity having been reached two days previously. This in turn was preceded by twenty-four hours by a peak in the excretion of porphobilinogen, which, again, was preceded by the institution of methionine therapy. These facts are probably entirely fortuitous, but it is possible that they are in part significant. Consider first the relation to the excretion of porphobilinogen. Waldenström and Vahlquist[22] (1944) have placed great stress on the significance of the excretion of porphobilinogen in these cases. It may be accepted that its presence in the urine is of diagnostic value. However, they go as far as to postulate formation from porphobilinogen of the porphyrin excreted in the urine. Waldenström and Vahlquist[23] (1939) have demonstrated the formation of porphyrin from porphobilinogen in vitro, and this has been confirmed by me[24] (1945). There is now the

22. Waldenström, J., and Vahlquist, B.: Acta med. Scandinav. **117**:1, 1944.
23. Waldenström, J., and Vahlquist, B.: Ztschr. f. physiol. Chem. **260**:189, 1939.
24. Prunty, F. T. G.: Biochem. J., to be published.

fact to be considered that uroporphyrin has been demonstrated in the feces and with the aid of ultraviolet microscopy and chemical isolation, in the liver, thus confirming the observations of Watson (Grinstein, Schwartz and Watson,[7] 1945; Watson, Schwartz and Hawkinson,[8] 1945). Furthermore, porphobilinogen is present in the liver (Prunty,[24] 1945). But a study of figure 4 does not lend support to a close correlation between the excretions of porphobilinogen and of uroporphyrin. There is no quantitative evidence of increased excretion of porphobilinogen in vivo, but there is a close relation between this substance and the production of pigment (porphobilin) (Prunty,[24] 1945). It is clear, therefore, that further evidence is required before the role of porphobilinogen can be determined, especially in relation to its place as a precursor from which the pathologic porphyrin is derived.

The effect of methionine in the present case is open to doubt. It has often been suggested that in acute porphyria abnormal porphyrin metabolism may take place in the liver (Mason, Courville and Ziskind,[9] 1933; Turner,[13] 1940). In some of the cases reported in the literature, as in the present example, histologic changes of the necrotic type in the cells of the liver with abnormal amounts of brown or yellow iron-free pigment have been noted (Palmer,[25] 1939-1940; Correll, Peters and Murphy,[26] 1942; Nesbitt and Watkins,[27] 1942). In addition, there are a few cases in which biochemical evidence suggestive of hepatic damage has been obtained during life (Turner,[28] 1938; Nesbitt and Watkins,[27] 1942). Evidence of this type has also been forthcoming in the present study. Whether the hepatic changes are cause or effect is still open to doubt, but there are some who hold the latter to be the case (Mason, Courville and Ziskind,[9] 1933). It is also true that hepatic damage, such as hepatitis and cirrhosis, usually leads to a rise in the urinary-fecal ratio of excretion of coproporphyrin, in which the increase is usually type I porphyrin (Dobriner and Rhoads,[12] 1940; Nesbitt and Snell,[29] 1942). Excretion of uroporphyrin in such conditions has not been reported. The data in table 2 are too incomplete for one to draw any definite conclusions, especially in view of the fact that it was only later discovered that ether extraction of acidified feces yielded only a portion of the coproporphyrin content. The figures, however, do not suggest a rise in fecal coproporphyrin during remission. It also appears from figure 4 that methionine did

25. Palmer, H. W.: Ann. Int. Med. **13**:1500, 1940.

26. Correll, H. L.; Peters, B. J., and Murphy, F. D.: Urol. & Cutan. Rev. **46**:341, 1942.

27. Nesbitt, S., and Watkins, C. H.: Am. J. M. Sc. **203**:74, 1942.

28. Turner, W. J.: Studies on Porphyria, Arch. Int. Med. **61**:762 (May) 1938.

29. Nesbitt, S., and Snell, A. M.: Excretion of Coproporphyrin in Hepatic Disease, Arch. Int. Med. **69**:573 (April) 1942.

not have any beneficial effect, but rather if it had any effect it was in the reverse direction. It is possible that it might have stimulated the production of porphyrin from some such precursor as proline by a process of methyl donation, direct carboxylation now being recognized as a biologic process (Best and Lucas,[30] 1945; Krebs,[31] 1943).

Relation of the Porphyrin Isomer Excreted to the Type of Porphyria.—Waldenström[32] (1934) was the first to report the occurrence of uroporphyrin III in nature, considering it to be typical of acute porphyria. Since that time considerable stress has been put on the fact that the production and the excretion of uroporphyrin I are typical of congenital porphyria and of uroporphyrin III typical of the acute type. It seemed likely, therefore, that the type of the excretion of porphyrin might be related to the symptomatology of the condition, type III porphyrin having less photodynamic activity than type I. However, since Waldenström's work the excretion of type I uroporphyrin in acute porphyria has been found (Turner,[24] 1938; Grinstein, Schwartz and Watson,[7] 1945). The latter authors have also shown that type I uroporphyrin predominates, whereas the type of coproporphyrin appears more variable. Porphobilinogen, however, is a characteristic product only in the acute porphyria (Watson, Schwartz and Hawkinson,[8] 1945). In addition, a mixture of the symptomatology of acute and congenital porphyria is known to occur together (Nesbitt and Watkins,[27] 1942). My patient showed the usual absence of photosensitivity, even under provocation, and no large excess of porphyrin in the plasma or cerebrospinal fluid. The results of the biochemical studies show that the uroporphyrin isolated from the urine yielded an ester with a melting point of 265 C. for the best preparation, in fact yielded a high percentage of coproporphyrin I, the ester melting at 245 C. It seems not unusual to be unable to remove by fractional crystallization the last impurity, on occasion a melting point not above 245 C. being obtainable for coproporphyrin I methyl ester (Rimington,[4] 1936; Watson, Schwartz and Hawkinson,[8] 1945), whereas the accepted melting point for pure coproporphyrin I is 252 C. In addition, the uroporphyrin urine contained porphyrin other than uroporphyrin I. The material could not be separated into uroporphyrin I and a type III porphyrin, found by Watson, Schwartz and Hawkinson[8] (1945) by absorption onto calcium carbonate and it therefore appeared to be a "Waldenström type B porphyrin," as classified by Watson. Decarboxylation either of the material isolated from the urine or of a specimen

30. Best, C. H., and Lucas, C. C., in Harris, R. S. and Thimann K. V.: Vitamins and Hormones, New York, Academic Press, Inc., 1943, vol. 1, p. 1.

31. Krebs, H. A., in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1943, vol. 12, p. 529.

32. Waldenström, J.: Acta med. Scandinav. **83**:281, 1934.

separated by chromatography from the "red-brown" impurity yielded finally the same product, mainly nearly pure coproporphyrin I. There was clear evidence of the presence of other porphyrins, but neither could type III porphyrin be isolated nor could the product of decarboxylation with a melting point of 219 to 226 C. be identified. Chromatography of the product from the first decarboxylation yielded a small amount of porphyrin, the melting point of the ester being 196 to 206 C. This may be a less pure form of Watson's heptamethyl ester with a melting point of 224 C. from which he obtained coproporphyrin I by further decarboxylation. The melting points of the esters of the small amounts of the uroporphyrin isolated from the liver and the feces (282 to 285 C. and 274 to 277 C. respectively) indicate that they were nearly pure uroporphyrin I octamethyl esters.

The coproporphyrin isolated from the urine and the feces was predominantly type I porphyrin, the feces yielding the purer specimen.

SUMMARY

Two cases of porphyria are recorded, one being the "latent type" of Waldenström. The other case exhibited the typical symptoms and course of acute porphyria.

Evidence of mild hepatic impairment was obtained. Histologic evidence of necrosis was found with deposits of brownish yellow granules in the cells of the liver in areas found by ultraviolet microscopic examination to contain porphyrin. The importance of the liver in the pathogenesis of the disease has been discussed.

Measurements of the excretion of coproporphyrin and uroporphyrin in the urine and the feces during two attacks are recorded. In addition, the excretion of porphobilinogen in the urine in one attack has been determined and its importance in relation to the formation of porphyrin examined.

A uroporphyrin described by Waldenström as type III has been isolated from the urine. This has been shown on further examination to be largely type I porphyrin.

Uroporphyrin I has also been obtained from the liver and the feces. Coproporphyrin I has been isolated from the urine and the feces.

Ultraviolet microscopic examination showed the presence of moderate amounts of porphyrin in the kidneys, especially the renal tubules, and in the costal cartilage. The emission spectrum suggested the latter may contain protoporphyrin.

The importance of the fact that type I porphyrins are found in both acute and congenital porphyrias has been indicated, and the added dif-

ficulties of explaining the differing symptomatology of these conditions have ben discussed.

Prof. C. Rimington helped with the material in this paper and stimulated discussion during the course of this work; Mr. J. Smiles and his assistants gave technical aid with the ultraviolet microscopic examination; Dr. R. Hilton permitted easy access to the patient under his care; Prof. W. G. Barnard expressed his opinion of the histologic material; Dr. S. C. Dobson conducted the postmortem examination, and the Central Research Fund, London University, gave a grant for the purchase of the Hilger absorptiometer used in this work.

PERIPHERAL BLOOD FLOW, RECTAL AND SKIN TEMPERATURE IN CONGESTIVE HEART FAILURE

The Effects of Rapid Digitalization in This State

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CLINICIANS have been under the impression that the skin of patients with congestive heart failure, especially the skin of the extremities, seemed cooler than normal even at a time when fever was present. Steele and Cohn [1] have made objective measurements relating to the temperature of the skin of certain areas of the body and to the rectal temperature in patients with heart failure in an attempt to arrive at an understanding of the fever which occurs in heart failure unrelated to any infection. They found that the "temperature of the surface in cardiac patients is lower than in normal individuals, while that of patients with infectious fever is as high as or higher than normal. The difference in behavior leads to the conclusion that the elevation of rectal temperature in heart failure depends on processes incidental to heart failure itself." [1a] Certain things are known about the circulation in heart failure and the effects of digitalis in this state. Stewart and Cohn,[2] Stewart, Deitrick, Crane and Wheeler,[3] Stewart, Crane, Watson,

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1. (*a*) Steele, J. M.: Fever in Heart Failure; Relations Between the Temperatures of the Interior and the Surface of the Body, J. Clin. Investigation **13**:869, 1934. (*b*) Cohn, A. E., and Steele, J. M.: Unexplained Fever in Heart Failure, ibid. **13**:853, 1934. (*c*) Steele, J. M.: Fever in Heart Disease, Internat. Clin. **1**:17, 1936.

2. Stewart, H. J., and Cohn, A. E.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: III. Part I. The Effect on the Output in Normal Human Hearts; Part II. The Effect on the Output of Hearts in Heart Failure with Congestion, in Human Beings, J. Clin. Investigation **11**:917, 1932.

3. Stewart, H. J.; Deitrick, J. E.; Crane, N. F., and Wheeler, C. H.: Action of Digitalis in Uncompensated Heart Disease, Arch. Int. Med. **62**:569 (Oct.) 1938.

Wheeler and Deitrick [4] and McGuire, Hauenstein and Shore [5] have shown that the cardiac output per minute and per beat of the heart is low in the presence of congestive heart failure and that the heart is dilated at a time when the velocity of blood flow is slow and the venous pressure elevated.[6] The exhibition of digitalis under those circumstances decreased the size of the heart and increased the volume output of blood from the heart per minute and per beat, resulting in an increase in velocity of blood flow and a fall in venous pressure.[6] Abramson, Fierst and Flachs,[7] using the method of venous occlusion in taking plethysmographic readings, found in patients with chronic congestive heart failure that the blood flow to edematous limbs was within the range of that observed in normal subjects. Certain experimental data pointed to a decrease in the amount of blood allotted to the peripheral blood flow in congestive heart failure, while others indicated a normal blood flow in the extremities. Objective measurements with respect to the total peripheral blood flow have not been available to clarify this question. To supply this information was the object of the observations now being reported.

MATERIAL

Studies were made of 15 patients suffering from heart failure before and after the exhibition of digitalis bodies. The drug was given intravenously in order that there might be a comparison of the peripheral blood flow immediately before injection with the flow at intervals immediately, as well as at longer intervals, afterward.

Strophanthin K was chosen [8] because its effects are detectable a matter of minutes after injection. Patients exhibiting auricular fibrillation as well as those with normal sinus mechanism were available for study, and those in the various etiologic categories of heart disease—namely, rheumatic, arteriosclerotic and hypertensive—were represented.

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4. Stewart, H. J.; Crane, N. F.; Watson, R. F.; Wheeler, C. H., and Deitrick, J. E.: The Cardiac Output in Congestive Heart Failure and in Organic Heart Disease, Ann. Int. Med. **13**:2323, 1940.

5. McGuire, J.; Hauenstein, V., and Shore, R.: Cardiac Output in Heart Disease Determined by the Direct Fick Method, Including Comparative Determinations by the Acetylene Method, Arch. Int. Med. **60**:1034 (Dec.) 1937.

6. Stewart and Cohn.[2] Stewart, Deitrick, Crane and Wheeler.[3] Stewart and others.[4]

7. Abramson, D. I.; Fierst, S. M., and Flachs, K.: Rate of Peripheral Blood Flow in the Presence of Edema, Am. Heart J. **25**:328, 1943.

8. (*a*) Brams, W. A.; Golden, J. S.; Sanders, A., and Kaplan, L. G.: Observations on Toxicity and Clinical Value of Strophanthin, Ann. Int. Med. **13**:618, (Oct.) 1939. (*b*) Eichna, L. W., and Taube, H.: A Comparison of the Action of Four Cardiac Glycosides on a Patient with Congestive Heart Failure, Am. Heart J. **26**:631, 1943; (*c*) The Effect of Intravenously Administered Digoxin and Ouabain on the Systemic Venous Pressure of Patients with Congestive Heart Failure, ibid. **27**:641, 1944.

In addition to strophanthin K, which is known to exhibit its effects shortly after injection, digitaline Nativelle, which can also be given intravenously, was used. This drug was chosen because it induces its effects more slowly.[5b] Nine patients were given strophanthin K; 2 of these patients received the drug on two occasions. Digitaline Nativelle was given to 8 patients.

PLAN OF OBSERVATIONS

All patients were admitted to the hospital and placed at complete rest in bed. The intake of fluid was usually limited to 1,200 cc. per day, and the intake of salt to 3 Gm. Before the drug was given, four sets of observations of rectal and skin temperatures were made from which three control levels of peripheral blood flow could be estimated. Blood pressure and heart rate were recorded between the other observations. Single basal metabolic rate, circulation time, venous pressure and electrocardiogram served as controls. Electrocardiograms were afterward made at intervals of ten to thirty minutes for all patients, except L. B., who were receiving strophanthin K; for only 2 patients given digitaline Nativelle (M.H. and E.P.) were electrocardiograms taken. After control observations were made, the drug selected for studying was given intravenously. Beginning fifteen minutes after the injection, all the observations were repeated at twenty minute intervals for seventy to one hundred and eighty minutes afterward, the average length of time being ninety-five minutes. In some instances measurements were made twenty-four to forty-eight hours later, as well as at longer intervals. All of the data on a patient secured before injection were averaged to give an estimate of the peripheral blood flow and other conditions prevailing before the injection of digitalis. All of the measurements taken after the injection for the morning were averaged and are recorded in the table; the maximum single peripheral blood flow recorded after injection is also shown. One or two basal metabolic rates were recorded after the injection of the digitalis preparation, for integration in the calculation of the peripheral blood flow. The longest continuous observations relating to the effects of the drug covered one hundred and eighty minutes. Observations were not continued beyond this time because patients might become restless and not be considered basal. For 1 patient given digitaline Nativelle, however, observations were started three hundred minutes after the injection and continued for one hour.

All observations were made in the morning with the patients in a basal metabolic state. Patients were brought to the constant temperature room on a stretcher and lay in bed, arms at sides, covered only with a sheet, for one hour in order to become adjusted to the room temperature of 25 C. and the humidity of 45 to 50 per cent.

Observations on Patients

Name, Sex, Age (Yr.)	Date	Amount of Drug Intravenously, Mg.	Time with Reference to Drug	Peripheral Blood Flow, Cc./M²/Min.	Maximum Peripheral Blood Flow; Min. After Drug, Cc./M²/Min.	Rectal Temperature, °C	Average Skin Temperature, °C	Temperature (Centigrade) of 1	2	3	4	5	6
E. N.	3/18/41	....	Before	97	.....	37.22	34.09	34.2	34.5	36.2	35.6	34.3	33.9
F	3/18/41	0.25	78 min. after	116	131 cc. 78 min.	37.46	34.12	35.1	35.7	36.7	35.1	34.2	32.8
58	4/ 7/41	....	28 days after	110	.....	37.50	33.86	34.8	35.1	35.6	34.2	34.3	34.5
J. R.	1/16/40	....	Before	5	.....	37.63	31.71	30.9	32.3	33.5	34.2	31.9	30.7
M	1/16/40	0.125	137 min. after	14	17 cc. 84 min.	37.59	31.94	31.2	33.2	34.0	34.3	32.3	30.9
41	1/17/40	....	Before	16	.....	37.14	32.66	30.7	33.7	34.4	34.1	32.9	32.3
	1/17/40	0.125	131 min. after	24	27 cc. 56 min.	37.05	32 45	30.8	32.7	34.5	34.4	32.3	31.0
	1/25/40	....	8 days after	57	.....	36.99	33.79	33.9	34.4	34.4	34.6	33.7	33.4
	2/ 3/40	....	17 days after	23	.....	37.20	32.68	33.5	34.3	33.9	34.2	32.8	32.6
E. P.	4/ 7/42	....	Before	31	.....	36.99	33.30	34.0	34.1	33.9	34.3	33.2	33.0
M	4/ 7/42	0.25	80 min. after	41	61 cc. 40 min.	36.92	33.01	34.1	34.4	33.9	34.3	32.4	33.4
68													
D. S.	4/ 8/42	....	Before	36	.....	37.29	32.96	34.5	34.6	34.7	33.9	32.5	31.9
F	4/ 8/42	0.25	65 min. after	52	74 cc. 65 min.	37.26	33.12	34.5	34.9	34.7	33.9	32.6	31.8
41	4/11/42	....	3 days after	43	.....	36.82	32.93	34.2	34.0	33.8	33.4	31.1	31.8
F. R.	9/16/41	....	Before	14	.....	37.89	32.48	32.9	33.2	33.2	33.8	33.1	32.6
M	9/16/41	0.25	60 min. after	38	70 cc. 60 min.	37.94	33.14	33.9	34.1	33.3	34.5	33.7	32.7
38	9/17/41	....	Before	14	.....	37.69	32.57	32.6	33.1	33.3	33.6	32.9	32.8
	9/17/41	0.25	67 min. after	36	58 cc. 67 min.	37.78	32.71	33.4	32.5	33.5	33.7	33.4	32.3
	10/ 6/41	....	19 days after	13	.....	37.39	33.10	33.7	34.1	33.5	33.8	33.6	33.4
M. H.	1/10/42	....	Before	21	.....	37.54	33.80	34.5	35.6	34.9	35.4	33.7	33.2
M	1/19/42	....	Before	4	.....	37.43	33.09	34.0	34.9	34.4	34.6	33.4	32.8
51	1/19/42	0.25	70 min. after	27	40 cc. 70 min.	37.52	33.67	34.6	35.4	35.4	35.3	33.8	33.4
M. W.	2/16/42	....	Before	46	.....	37.38	33.58	34.0	34.7	34.6	34.3	33.9	33.4
M	2/16/42	0.25	73 min. after	90	99 cc. 73 min.	37.37	33.61	33.5	34.7	35.0	35.1	34.1	33.4
63	2/28/42	....	12 days after	83	.....	37.26	34.12	34.3	34.8	34.9	35.2	34.2	34.2
V. L. B.	7/14/42	....	Before	31	.....	37.68	33.23	34.0	35.0	34.9	35.2	33.6	32.6
F	7/14/42	0.125	180 min. after	84	148 cc. 50 min.	37.61	32.93	33.4	34.5	34.7	34.7	33.4	32.3
20	7/20/42	....	6 days after	22	.....	37.96	32.02	32.2	33.5	33.9	33.3	31.9	31.7
	7/21/42	....	7 days after	28	.....	36.18	32.22	32.9	33.8	34.3	33.6	32.2	32.4
L. B.	5/23/44	....	Before	27	.....	38.29	32.75	34.5	35.3	35.1	33.1	32.6	32.4
F	5/23/44	0.125	130 min. after	33	{ 61 cc. 30 min. / 60 cc. 70 min. }	38.38	32.77	34.7	35.1	35.1	33.3	32.9	32.4
38	5/25/44	....	2 days after	20	.....	38.16	31.90	33.6	33.1	33.8	32.2	30.3	32.4
Average Before				29	.....	37.56	32.95	33.3	34.0	34.4	34.2	33.1	32.6
Average After				50	71 cc. 64 min.	37.53	33.07	33.6	34.4	34.6	34.4	33.2	32.4

Observations on Patients

F. L.	5/26/43	....	Before	33	.....	37.11	33.48	35.0	34.8	34.6	35.0	33.9	33.6
M	5/26/43	1.2	110 min. after	53	88 cc. 110 min.	37.12	33.37	34.9	35.1	34.8	34.9	33.9	33.8
54	5/27/43	....	24 hrs. after	16	.....	37.04	33.47	34.4	34.6	34.2	34.5	33.7	33.9
	5/29/43	....	3 days after	13	.....	37.11	33.14	34.4	34.3	33.9	34.2	33.0	33.4
	6/ 3/43	....	7 days after	29	.....	37.58	33.41	34.4	34.6	34.1	34.3	33.5	33.7
M. O'S.	6/ 9/43	.....	Before	60	.....	37.48	33.40	34.6	34.3	34.2	34.5	33.3	33.6
M	6/ 9/43	1.2	112 min. after	51	49 cc. 92 min.	37.60	33.36	34.5	34.1	34.1	34.6	32.9	33.6
39	6/10/43	....	24 hrs. after	27	.....	37.72	33.23	34.9	34.5	34.4	34.6	33.2	34.0
N. K.	3/15/44	....	Before	25	.....	37.55	31.74	32.0	33.4	32.2	31.7	31.1	32.4
F	3/15/44	1.2	90 min. after	25	44 cc. 73 min.	37.64	31.66	32.2	33.3	32.2	31.6	30.9	32.0
55	3/23/44	....	8 days after	33	.....	37.07	32.13	33.1	33.6	33.4	31.9	31.8	32.6
	4/ 8/44	....	24 days after	56	.....	37.08	32.58	34.2	34.2	33.8	31.7	32.7	32.4
	4/10/44	....	26 days after	33	.....	37.11	32.00	33.4	33.6	33.4	31.4	32.2	31.9
K. H.	3/28/44	....	Before	51	.....	37.29	33.20	34.3	34.4	34.2	32.8	33.5	33.3
F	3/28/44	1.2	133 min. after	42	63 cc. 53 min.	37.52	33.33	34.4	34.4	34.6	33.3	34.0	33.2
75	3/30/44	....	2 days after	54	.....	37.35	33.29	34.0	34.3	34.5	33.5	33.3	33.6
M. M.	3/18/44	....	Before	59	.....	37.82	33.66	33.5	35.3	35.3	34.7	33.6	32.8
F	3/18/44	1.2	90 min. after	51	70 cc. 90 min.	37.93	33.52	33.7	35.1	35.1	34.6	33.4	33.1
60													

Given Strophanthin K

Eleven Areas on Body Surface					Heart Rate,* per Min.	Pulse Rate per Min.	Blood Pressure, Mm. Hg.	Basal Metabolic Rate, per Cent	Circulation Time, Sec.	Venous Pressure, Mm. Saline	Diagnosis
7	8	9	10	11							
33.9	34.0	33.5	32.6	30.9	83	90	170/112	+36	25	133	Hypertensive and arteriosclerotic heart disease; enlarged heart; auricular fibrillation; congestive heart failure.
33.9	34.2	33.0	32.5	30.2	87	84	183/113	+36	22	132	
34.1	32.9	32.8	32.9	30.7	73	68	188/97	+28	18	84	
28.4	33.2	31.8	30.8	26.5	150	76	.....	+25	52	246	Rheumatic heart disease; mitral stenosis and insufficiency; functional tricuspid insufficiency; enlarged heart; auricular fibrillation; congestive heart failure.
27.1	33.7	32.1	31.0	27.0	156	..	.....	+23	68	248	
32.9	33.1	31.3	31.3	30.3	130	80	.....	+13	68	280	
32.0	33.5	31.3	31.2	28.9	136	101	.....	+22	40	218	
34.6	33.5	32.7	32.7	34.0	89	88	135/88	+ 6	46	242	
33.5	32.3	31.3	29.8	31.8	72	69	119/65	+ 5	31	62	
34.3	32.7	32.0	32.1	32.9	59	60	170/97	+10	35	70	Hypertensive and arteriosclerotic heart disease; enlarged heart; normal rhythm; congestive heart failure.
33.5	32.4	31.6	31.4	32.1	65	61	165/95	+ 7	35	75	
34.2	31.5	30.7	31.3	32.8	91	97	170/127	+ 6	22	80	Hypertensive heart disease; enlarged heart; normal rhythm; congestive heart failure.
33.7	31.6	30.7	31.8	33.6	83	84	163/124	— 9	17	68	
34.0	31.7	31.6	32.6	33.2	86	72	169/110	— 7	13	100	
33.2	31.5	30.9	31.0	32.6	115	116	180/145	+25	..	...	Hypertensive heart disease; enlarged heart; normal rhythm; congestive heart failure.
33.8	31.7	31.4	31.2	33.7	112	111	180/140	+35	24	233	
33.2	31.8	31.6	31.1	33.1	100	105	168/138	+13	20	210	
33.3	31.8	31.5	31.1	33.0	108	107	163/141	+24	20	209	
33.4	32.5	31.9	31.9	32.6	75	79	171/123	+ 1	13	67	
34.3	33.1	31.7	32.2	32.9	95	105	100/80	+ 7	46	243	Hypertensive heart disease; enlarged heart; angina; normal rhythm; congestive heart failure.
34.0	32.6	31.6	31.2	29.7	94	106	102/80	+ 3	56	242	
34.4	33.0	31.8	31.7	31.7	86	91	104/82	+ 3	44	165	
34.3	32.7	31.4	32.9	33.2	77	80	146/85	+35	23	84	Pulmonary heart disease; cor pulmonale; pulmonary fibrosis and emphysema; chronic bronchitis; enlarged heart; normal rhythm; congestive heart failure.
34.1	32.5	31.2	32.7	33.0	80	77	141/79	+44	20	80	
34.5	32.8	33.2	32.4	33.6	..	71	156/89	+19	16	62	
32.7	34.0	31.5	30.7	30.4	120	92	113/71	+33	28	119	Rheumatic heart disease; mitral stenosis and insufficiency; enlarged heart; auricular fibrillation; congestive heart failure.
32.5	33.6	31.3	30.4	29.9	118	79	112/72	+29	25	72	
32.3	32.5	29.7	30.0	30.7	78	65	133/94	+ 8	..	...	
32.9	31.8	29.2	30.0	30.4	72	62	135/95	+ 6	33	64	
34.1	30.9	31.3	30.7	30.2	124	78	92/64	+32	..	...	Rheumatic heart disease; mitral stenosis and insufficiency; enlarged heart; auricular fibrillation; congestive heart failure.
33.7	31.1	31.7	30.7	29.9	106	65	102/60	+30	..	...	
34.6	29.6	29.5	30.0	33.6	146	79	107/61	+24	..	...	
33.2	32.5	31.6	31.4	31.1	104	89	119/84	+21	37	163	
32.9	32.6	31.6	31.5	31.2	104	76	119/82	+22	33	158	

Given Digitaline Nativelle

34.7	33.8	30.9	31.2	31.2	90†	84	108/77	+25	..	...	Rheumatic and arteriosclerotic heart disease; mitral stenosis and insufficiency; enlarged heart; auricular fibrillation; congestive heart failure.
34.2	33.3	30.5	31.0	30.2	..	73	112/77	+31	..	...	
34.2	33.6	31.5	31.6	32.6	..	59	112/74	+24	..	...	
34.3	32.7	31.1	31.7	31.7	75	60	107/72	+11	..	...	
34.6	33.2	31.1	31.8	32.9	..	62	111/71	+19	..	...	
34.3	33.5	32.5	31.9	30.8	100	90	94/66	+22	..	...	Rheumatic heart disease; mitral stenosis and insufficiency; auricular fibrillation; no signs of heart failure.
34.4	33.0	32.1	32.0	31.9	96	79	96/66	+22	..	...	
34.5	33.3	31.4	31.8	28.6	..	78	96/60	+17	..	...	
33.6	30.9	30.5	30.7	31.4	124	118	164/92	+49	..	...	Hypertensive and arteriosclerotic heart disease; enlarged heart; auricular fibrillation; heart failure.
33.3	30.6	30.2	30.9	31.7	113	101	174/107	+56	..	...	
33.4	31.2	30.8	31.2	30.6	76	73	128/83	+23	..	...	
33.9	31.4	31.1	31.5	32.2	86	79	123/79	+36	..	...	
33.2	30.9	30.7	31.0	30.9	78	70	133/78	+37	..	...	
34.9	31.8	31.7	31.8	33.9	85	84	142/67	+28	..	...	Hypertensive and arteriosclerotic heart disease; enlarged heart; auricular fibrillation; no signs of heart failure.
34.8	31.9	31.3	31.8	34.1	83	82	164/65	+33	..	...	
35.0	32.0	31.4	31.8	34.1	74	74	154/67	+31	..	...	
33.7	33.5	33.2	32.3	30.7	101	94	123/72	+31	..	...	Arteriosclerotic heart disease; enlarged heart; auricular fibrillation; congestive heart failure.
34.1	32.7	32.6	32.3	31.0	85	83	144/68	+31	..	...	

Name, Sex, Age (Yr.)	Date	Amount of Drug Intravenously, Mg.	Time with Reference to Drug	Peripheral Blood Flow, Cc./M²/Min.	Maximum Peripheral Blood Flow; Min. After Drug, Cc./M²/Min.	Rectal Temperature, °C	Average Skin Temperature, °C	Temperature (Centigrade) of 1	2	3	4	5	6
W.M.	4/ 1/44	....	Before	35	.....	37.23	33.60	35.0	34.8	34.2	35.0	33.4	33.1
M	4/ 1/44	1.2	132 min. after	36	70 cc. 112 min.	37.16	33.55	34.7	35.4	34.4	33.5	34.0	33.2
45	4/ 3/44	....	2 days after	21	.....	37.85	33.06	34.5	34.3	34.1	34.6	32.9	32.4
M. H.	1/22/42	....	Before	12	.....	37.22	33.23	34.0	34.6	34.4	34.8	33.2	33.2
M	1/22/42	1.2	5 hrs. after	93	97 cc. 5 hrs.	37.26	34.50	35.1	35.5	35.8	35.7	33.8	33.3
51													
E. P.	4/10/42	....	Before	19	.....	37.00	33.02	34.3	34.1	33.5	33.8	32.7	32.5
M	4/10/42	1.2	70 min. after	25	36 cc. 80 m.n.	37.00	33.71	34.2	34.9	33.2	33.7	32.4	32.3
68	4/10/42	....	150 min. after	36	.....	36.85	32.95	34.3	33.9	33.4	33.9	32.9	32.9
Average Before				37	.....	37.34	33.17	34.1	34.6	34.2	34.0	33.1	33.2
Average After				48	65 cc. 114 min.	37.40	33.20	34.2	34.7	34.3	34.0	33.2	33.2
Average of all patients before digitalis bodies			19 measurements on 15 patients	32	.....	37.44	33.03	33.6	34.2	34.3	34.2	33.1	32.8
Average of all patients after digitalis bodies			19 measurements on 15 patients	49	.....	37.50	33.19	33.9	34.5	34.4	34.3	33.2	32.8
Normal subjects at 25 C.[20]			25 measurements on 24 patients	33	.....	36.72	32.82	33.92	33.66	33.44	33.59	32.67	32.45

* These rates were calculated from electrocardiograms and were not synchronous with the pulse rates, which
† Electrocardiograms were not taken during these observations except in the case of E. P., and the rates in this

The blood pressure cuff placed on the patient's left arm and electrodes for deriving the electrocardiograms remained in place throughout the morning.

Of strophanthin K.[9] 0.25 mg. was given intravenously to all patients except those with mitral stenosis, to whom half of this amount, namely, 0.125 mg., was administered. Of digitaline Nativelle 1.2 mg. was given intravenously. The injections were given slowly, five to ten minutes being required for injection. The following patients given strophanthin K had normal rhythm: M.H., E.P., D.S., F.R. and M.W.; the following had auricular fibrillation: L.B., V.B., E.N. and J.R. Of those patients given digitaline Nativelle, M.H. and E.P. had normal rhythm and F.L., M.O'S., N.K., K.H., M.M. and W.M. had auricular fibrillation.

METHODS

The peripheral blood flow was measured by our modification[10] of the method of Hardy and Soderstrom.[11] In this method the average peripheral blood flow for the whole body is estimated as cubic centimeters per square meter of the body surface per minute, rather than the

9. The Abbott Laboratories supplied the strophanthin K used in these studies.

10. Stewart, H. J., and Jack, N. B.: The Effect of Aminophyllin on Peripheral Blood Flow, Am. Heart J. **20**:205, 1940. Stewart, H. J., and Evans, W. F.: Peripheral Blood Flow in Myxedema, Arch. Int. Med. **69**:808 (May) 1942.

11. Hardy, J. D., and Soderstrom, G. F.: Heat Loss from the Nude Body and Peripheral Blood Flow at Temperatures of 22° C. to 35° C., J. Nutrition **16**:493, 1938.

on the Skin and Rectal Temperatures in Patients with Congestive Heart Failure—Continued

Eleven Areas on Body Surface					Heart Rate,* per Min.	Pulse Rate per Min.	Blood Pressure, Mm. Hg.	Basal Metabolic Rate, per Cent	Circulation Time, Sec.	Venous Pressure, Mm. Saline	Diagnosis
7	8	9	10	11							
35.0	32.7	32.1	31.4	33.7	92	83	104/78	+ 3	..	...	Postoperative chronic constrictive pericarditis; enlarged heart; auricular fibrillation; heart failure.
34.6	32.6	31.9	30.9	33.5	90	84	112/71	+ 3	..	...	
34.1	32.5	31.7	31.3	31.4	72	70	97/67	+ 2	..	..	
33.2	33.8	33.0	31.6	30.0	..	97	117/82	+ 5	49	184	Hypertensive heart disease; enlarged heart; angina; normal rhythm; congestive heart failure.
34.5	34.0	33.6	33.0	34.3	..	100	126/86	+ 8	51	161	
34.5	32.7	31.1	31.4	32.0	68	68	175/113	+ 6	33	112	Hypertensive and arteriosclerotic heart disease; enlarged heart; normal rhythm; congestive heart failure.
34.7	31.7	31.0	31.0	32.6	68	68	173/104	+13	32	112	
34.5	32.4	31.2	31.0	32.0	..	68	178/113	....	33	100	
34.2	32.8	31.9	31.5	31.7	94	90	128/81	+21	..	...	
34.3	32.5	31.7	31.6	32.4	87	73	138/81	+25	..	...	
33.6	32.7	31.7	31.5	31.4	95	89	123/82	+21	..	...	
33.5	32.6	31.5	31.5	31.7	93	70	127/82	+23	..	...	
33.59	32.89	32.11	32.22	30.91	..	..	.....	— 3	..	...	

accounts for discrepancies in rates.
column are apical heart rates.

blood flow prevailing in local areas. Measurements were made at twenty minute intervals except in the case of V.B., for whom they were made at ten minute intervals, and in that of J.R., for whom the intervals varied.[12] For the estimation of peripheral blood flow by this method recordings were made (*a*) of the temperature of the skin from 11 areas on the surface of the body (fig. 1), by means of the Hardy radiometer [13]; (*b*) of the rectal temperature by means of a copper-constantan thermocouple [11]; (*c*) of the basal metabolic rate with a Benedict-Roth apparatus.[14] The tables of Du Bois and Du Bois [15] were used in estimating the surface area, and of the Mayo Clinic [16] in calculating the basal metabolic rate.

The circulation time was measured with dehydrocholic acid [17] and the venous pressure by the direct method of Taylor, Thomas and

12. In the calculations the formulas allow for such variations.

13. Hardy, J. D., and Soderstrom, G. F.: An Improved Apparatus for Measuring Surface and Body Temperature, Rev. Scient. Instruments **8**:419, 1937.

14. Roth, P.: Modifications of Apparatus and Improved Technique Adaptable to the Benedict Type of Respiration Apparatus, Boston M. & S. J. **186**:457, 1922.

15. Du Bois, D., and Du Bois, E. F.: A Formula to Estimate Approximate Surface Area if Height and Weight Be Known, Arch. Int. Med. **17**:863 (June) 1916.

16. Boothby, W. M.; Berkson, J., and Dunn, H. J.. Studies of the Energy of Metabolism of Normal Individuals: A Standard for Basal Metabolism, with a Nomogram for Clinical Application, Am. J. Physiol. **116**:468, 1936.

17. Tarr, L.; Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, Am. Heart J. **8**:766, 1933.

Schleiter.[18] Both these measurements were made in free intervals, with only one venipuncture and without a tourniquet, at such a time that basal conditions were restored by the time the interval had arrived for recording the skin and rectal temperatures. This precaution was taken

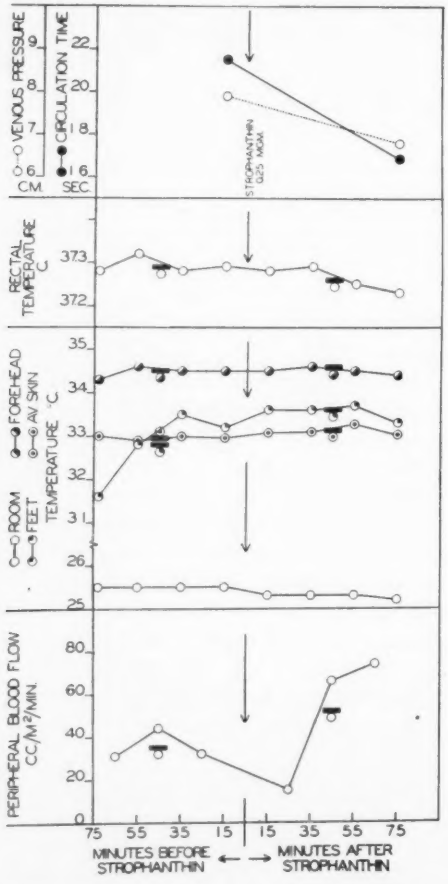

Fig 1.—In this figure are recorded the data relating to D.S. showing the effect on the peripheral blood flow and skin and on the skin and rectal temperatures, venous pressure and circulation time, of the administration of 0.25 mg. of strophanthin K. The averages of the measurements before and after injection of the drug are shown by appropriate symbols attached to a black bar.

18. Taylor, F. A.; Thomas, A. B., and Schleiter, H. G.: A Direct Method for the Estimation of Venous Blood Pressure, Proc. Soc. Exper. Biol. & Med. **27**:867, 1930.

in case there had been any emotional response to the venipuncture and the bitter taste of the dehydrocholic acid.

OBSERVATIONS

There were 11 observations of 9 patients relating to strophanthin K. The results for 1 patient (D.S.) serve to illustrate the effects of this

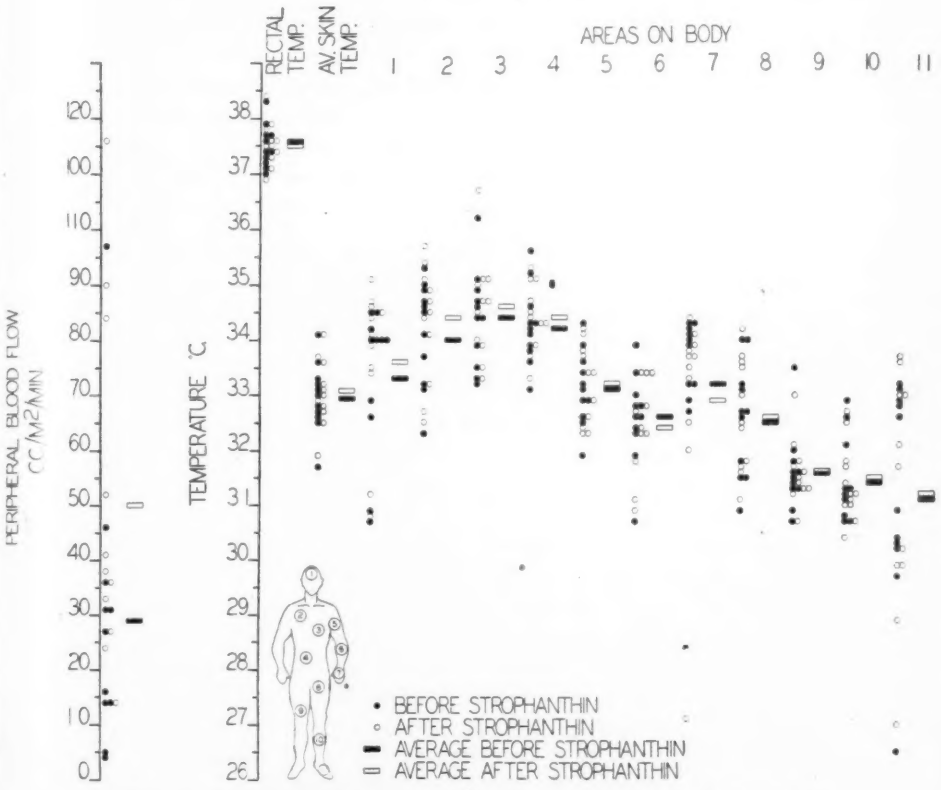

Fig. 2.—In this figure are recorded the data relating to patients given strophantin K. The closed circles indicate the average of each patient's measurements before, and the open circles the average of the measurements made on the same morning after, the administration of strophanthin K. The averages of all the patients before and after the administration of strophanthin K are represented by the solid and open bars respectively.

drug (table 1, fig. 1). The results for all patients are shown in the table and in figure 2.

The Peripheral Blood Flow, Skin and Rectal Temperatures in Congestive Heart Failure.—The average of the peripheral blood flow

for all patients during heart failure was 32 cc. per square meter per minute, that is to say, in the normal range (the table and fig. 2), as compared to 33 cc. per square meter per minute [19] for normal subjects at the same room temperature of 25 C.[20] The rectal temperature was higher than normal, and the average skin temperature was slightly warmer than normal. The temperature of the forehead (area 1) and lower part of the thigh and leg (areas 9 and 10) was slightly cooler than normal, while for all the other areas it was warmer than normal, except for the hand (area 7), which was the same.

The Effects of Strophanthin K on Peripheral Blood Flow, Rectal and Skin Temperatures in Congestive Heart Failure.—The peripheral blood flow was 36 cc. per square meter per minute, in short, in the normal range [21] in D. S., although this patient had congestive heart failure (fig. 1). The rectal temperature was elevated to 37.29 C. (99.37 F.), and the average weighted skin temperature was slightly increased, 32.96 C. (91.29 F.). After the injection of 0.25 mg. of strophanthin K intravenously the peripheral blood flow increased, the rectal temperature fell, the average weighted skin temperature rose and the feet became warmer. The average peripheral blood flow during the sixty-five minutes after injection was 52 cc. per square meter per minute, while the maximum of 74 cc. per square meter per minute was attained sixty-five minutes after injection. The heart rate became slower, the circulation time fell from twenty-two seconds to seventeen seconds and the venous pressure, which was not elevated, fell from 80 mm. to 68 mm.

The results for all the patients are plotted in figure 2 (see also the table). The averages for all the patients showed that the peripheral blood flow increased from 29 cc. per square meter per minute to 50 cc. per square meter per minute after injection, and the average maximal effect over the period of the observations was 71 cc. per square meter per minute for the sixty-four minute period. The rectal temperature fell. The average weighted skin temperature and temperature of the upper part of the body rose slightly.

The Effects of Digitaline Nativelle on Peripheral Blood Flow and Rectal and Skin Temperatures in Congestive Heart Failure.—The effects of giving 1.2 mg. of digitaline Nativelle intravenously were

19. This figure is lower than in the original paper because only one measurement concerning each patient was averaged.

20. Stewart, H. J.; Haskell, H. S., and Evans, W. F.: The Peripheral Blood Flow and Other Observations in Coarctation of the Aorta, Am. Heart J. **28**:217, 1944.

21. Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow Under Basal Conditions in Normal Male Subjects in the Third Decade, Am. Heart J. **26**:67, 1943.

similar to those following the giving of strophanthin K, except that over the time observations were made the increase in peripheral blood flow was less noticeable and the effects were slower in appearing (see the table). The peripheral blood flow increased from 37 cc. per square meter per minute to 49 cc. per square meter per minute. The average maximal peripheral blood flow was 65 cc. per square meter per minute for one hundred and fourteen minutes after injection, as compared with 74 cc. per square meter per minute for sixty-four minutes after the giving of strophanthin K (see the table). There was for this group, after the use of digitaline Nativelle, a slight rise in rectal temperature, a very slight rise in average weighted skin temperature and no significant change in the temperature of the individual areas of the body except of the feet, which was increased. In this group of patients during failure the peripheral blood flow was higher than in the strophanthin K group, and the average weighted skin temperature higher and the rectal temperature lower. This group included 2 patients (M. O'S. and K. H.) who had no signs of heart failure at the time these observations were made.

We have compared the effects of strophanthin K and digitaline Nativelle for 2 patients (M. H. and E. P., table 1). For one, E. P., observations made at comparable times after injection of the two drugs showed that strophanthin K induced its effects more rapidly than did digitaline Nativelle (see the table).

COMMENTS

These observations have shown that during heart failure the peripheral blood flow is in the normal range as compared with the peripheral blood flow in normal subjects at the same environmental temperature.[20] The average weighted skin temperature of the body was slightly increased. The rectal temperature was elevated. The forehead was slightly cooler than normal. The hands were of the same temperature and the feet warmer than those of normal persons at the same room temperature. Sixty-four minutes after the injection of strophanthin K the peripheral blood flow increased; for the whole group the maximum effect on peripheral blood flow was recorded sixty-four minutes after injection, when it was 71 cc. per square meter per minute (see the table). When all the observations for all patients for corresponding times are averaged and plotted, a curve is shown for the initiation of effects on the peripheral blood flow (fig. 3). On this curve the maximal increase to 66 cc. per square meter per minute was obtained in sixty minutes for strophanthin K. The average weighted skin temperature increased, and the rectal temperature fell. On the average, the temperature of most of the areas of the body increased and of the hands and forearms decreased slightly (fig. 1). At this time there was slowing

of the heart rate, the circulation time was shorter and the venous pressure less.

How can these results be correlated with the other known effects of digitalis? In observations of Stewart and Cohn, the cardiac output was decreased and the heart dilated in dogs whose hearts had been made to fibrillate.[22] Forty-five minutes after tincture of digitalis had been given intravenously, decrease in size of the heart and increase in cardiac output occurred. Digitalis induced similar results in a dog [22] in which, by ingestion of bromide, edema had been induced, which was associated with decrease in cardiac output and increase in cardiac

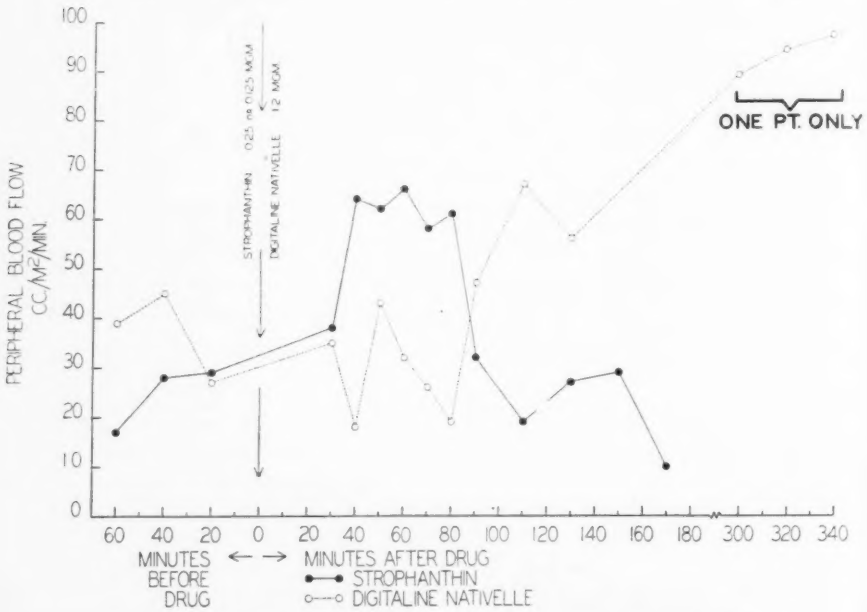

Fig. 3.—In this figure are recorded the effects on peripheral blood flow of strophanthin K and digitaline Nativelle. All the measurements of all patients receiving each drug were averaged for each time interval before and after injection, so that a curve is obtained. The last 3 circles on the digitaline Nativelle curve represent measurements of only 1 patient.

size, since increase in cardiac output and decrease in cardiac size occurred twenty-four hours after digitalis had been given intravenously. Similar results were recorded by Stewart, Deitrick, Crane and

22. Stewart, H. J., and Cohn, A. E.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: II. The Effect on the Output of Hearts of Dogs Subject to Artificial Auricular Fibrillation, J. Clin. Investigation **11**:897, 1932.

Thompson [23] when the drug was given by mouth to patients with auricular fibrillation. Also in patients with heart failure to whom the drug was given by mouth, increase in output and decrease in size of the heart [6] could be detected as early as nine hours after administration. Moreover, in normal subjects when the drug was given by mouth, effects on cardiac output and on cardiac size [2] were observed as early as nine hours. Stewart and Cohn [2] and Stewart [24] and others [5] have shown that the volume output of blood from the heart is decreased during heart failure and that as early as nine hours after digitalis has been given by mouth an increase in cardiac output has occurred. In short, in all of these there is ample evidence that the volume output of blood is decreased in congestive heart failure and that the effect of digitalis is to increase the volume of blood expelled by the heart. These effects may now be correlated with those relating to peripheral blood flow. At a time when the cardiac output is low during failure or as a consequence of auricular fibrillation,[25] the peripheral blood flow is in the normal range; in short, in the face of the decreased output of blood from the heart, a normal amount is, nevertheless, allotted to the peripheral circulation. The average skin temperature of the body is warmer than normal. The rectal temperature is elevated in heart failure. One explanation of these events is as follows: During heart failure the volume of blood allotted to the peripheral circulation in unit time is in the normal range, but it moves so slowly in a distended vascular bed in which there is an increased volume of circulating blood [26] that it is probably insufficient to eliminate heat from the body; the rectal temperature rises as a consequence. Other adjustments, such as increase in heat lost in moisture by way of the lungs, are brought into use and prevent to some extent a greater rise in internal temperature. With the exhibition of strophanthin K, the peripheral blood flow increases within sixty-four minutes, the average weighted skin temperature increases, and the rectal temperature falls slightly. In short, with the increase in cardiac output which has been brought

23. Stewart, H. J.; Dietrick, J. E.; Crane, N. F., and Thompson, W. P.: Studies of the Circulation in the Presence of Abnormal Cardiac Rhythms: Observations Relating to (Part I) Rhythms Associated with Rapid Ventricular Rate, and to (Part II) Rhythms Associated with Slow Ventricular Rate, J. Clin. Investigation **17**:449, 1938.

24. Stewart, H. J.; Deitrick, J. E.; Watson, R. F.; Wheeler, C. H., and Crane, N. F.: The Effect of Valvular Heart Disease on the Dynamics of Circulation, Am. Heart J. **16**:477, 1938. Stewart, Deitrick, Crane and Wheeler.[3] Stewart and others.[4]

25. Stewart and Cohn.[2] Stewart, Deitrick, Crane and Wheeler.[3] Stewart, Deitrick, Crane and Thompson.[23]

26. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: III. Changes in Blood Volume, Venous Pressure and Blood Velocity Rate in Chronic Congestive Heart Failure, J. Clin. Investigation **16**:851, 1937.

about by strophanthin K, an increased amount is available and is distributed to the periphery of the body; with more blood brought to the periphery the average skin temperature and temperature of most of the areas of the skin becomes higher. With the increased amount of blood available to the skin surface for radiation of heat the rectal temperature falls.

The highest peripheral blood flow after the administration of strophanthin K was recorded sixty-four minutes after the drug was given, while the highest after the administration of digitaline Nativelle occurred later, namely one hundred and fourteen minutes afterward. There were no significant changes in the peripheral blood flow sixty-four minutes after the administering of digitaline Nativelle. The difference in the time at which the effects of strophanthin K and digitaline Nativelle are evident is shown in figure 3, in which all the measurements of peripheral blood flow at corresponding times before and after injection are averaged and plotted for each of the two drugs. It is apparent that the peripheral blood flow increases forty minutes after injection of strophanthin K and remains elevated for eighty minutes after injection, and then decreases. On the other hand there are no significant changes after the administration of digitaline Nativelle at this time, but the increase begins about ninety minutes after injection and is still present one hundred and thirty minutes afterward. In 1 patient in whom observations were made five hours after injection the peripheral blood flow was still higher than the control levels.

These results following the exhibition of digitalis bodies are different from those recorded by Eichna and Taube,[8b] who found that the return of venous pressure and ventricular rate to normal was not accompanied with a significant alteration in the volume of blood flow to the resting hand and calf; they used a plethysmographic method. The method my colleagues and I have used records the average peripheral blood flow allotted to the periphery of the whole body in cubic centimeters per square meter per minute for a depth of 1 cm., rather than the flow in isolated areas.

In 2 patients (M. H. and E. P.) the effects of strophanthin K and of digitaline Nativelle were compared. The results were similar to those in which the large groups of individual patients were compared.

The basal metabolic rate was increased in many of these patients, which is not uncommon in heart failure.[27] When the peripheral blood flow is plotted against the corresponding basal metabolic rate before and after the administering of digitalis, a rough linear correlation is apparent, in that the higher peripheral blood flow occurred in those patients with the higher basal metabolic rate and the lower peripheral

27. Stewart, H. J., and Jack, N. B.: The Basal Metabolic Rate in Organic Heart Disease, Am. Heart J. **19**:738, 1940.

blood flow occurred in those with the lower basal metabolic rate. In short, patients with a basal metabolic rate in the normal zone had lower peripheral blood flow, and the ones with a higher basal metabolic rate had higher peripheral blood flow, but not as high as it would have been for the corresponding increases in basal metabolic rate which occur in hyperthyroidism.[28]

Our results with respect to skin temperatures for the areas of the body are unlike those of Steele and Cohn [1ab] in that in our patients with heart failure we found no definite change on the average in the local temperature, although in certain patients this was the case. They measured skin temperatures in fewer areas than we did. If our patients had exhibited more pronounced heart failure the results might not have been so divergent. On the other hand, Abramson, Fierst and Flachs [7] found the blood flow to edematous limbs within the range of that obtained in normal subjects, results comparable to ours, namely, that the blood flow allotted to the whole periphery is in the normal range for the environmental temperature. The rectal temperature was elevated. This, we think, is due to the inability of the body, with the volume of blood allotted to the periphery—although this is normal in amount—to eliminate enough heat by this route. The blood moves at a slower velocity because of the increased size of the vascular bed and increased volume of blood. For the higher level of basal metabolic rate the amount is insufficient to eliminate heat adequately, and rise in rectal temperature occurs. Peripheral cyanosis is one visual evidence of the decrease in velocity of blood flow in heart failure. A linear correlation was not apparent when the average weighted skin temperature was plotted against the corresponding rectal temperatures.

SUMMARY

The peripheral blood flow has been measured in patients exhibiting congestive heart failure before and after the administration of strophanthin K and digitaline Nativelle intravenously. A modification [10] of the Hardy-Soderstrom method was used.[13] Measurements of rectal and of skin temperature were recorded. Electrocardiograms were taken at appropriate intervals. Circulation time and venous pressure were measured in order that there might be other data to correlate with the measurements of the peripheral blood flow. These effects have been discussed in relation to another known effect of digitalis bodies, namely, their effect on cardiac output. It appears that:

1. The amount of blood flow allotted to the whole periphery of the body is in the normal range during heart failure as compared with

28. Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow in Hyperthyroidism, Am. Heart J. **20**:715, 1940.

the amount in normal subjects at the same environmental temperature. Although the volume output of blood from the heart is decreased in heart failure, there is no apparent restriction in the amount of blood allotted to the peripheral circulation.

2. The average weighted skin temperature is slightly increased in heart failure; the forehead is slightly cooler, and the feet are slightly warmer than normal; the temperature of the other areas of the skin is in the normal range.

3. Even though the same amount of blood is allotted the peripheral circulation in heart failure, it is insufficient, because of its slowed velocity in a vascular tree that is dilated, to maintain an adequate elimination of heat in the face of the metabolic demands, so that the internal temperature of the body (rectal temperature) rises.

4. After the administration of strophanthin K intravenously, the peripheral blood flow increases. The volume output of blood from the heart having been increased by digitalis, more blood is now available for the peripheral circulation. With the allocation of more blood to the periphery, the temperature of the skin rises and the feet become warmer still. The body can now lose more heat by way of the skin and its internal temperature (rectal temperature) falls slightly but does not usually reach normal levels over the intervals studied.

5. Similar results were observed following the intravenous injection of digitaline Nativelle.

6. The effects were observed from forty to sixty minutes after the administration of strophanthin K, but were slower, namely eighty minutes, in appearing after the administration of digitaline Nativelle. This difference in time in which effect on peripheral blood flow occurs is in agreement with observations of others, which showed that, molecule for molecule, ouabain initiated effects more rapidly and digitaline Nativelle more slowly.

PATENT DUCTUS ARTERIOSUS WITH SUBACUTE BACTERIAL ENDARTERITIS

Diagnosis and Indications for Operation

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AND
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NEW YORK

LIGATION of the patent ductus arteriosus was first proposed in 1907, by Munro.[1] He had seen a healthy infant die of this cardiac anomaly. Based on the observations at autopsy and other anatomic studies, he described in detail an operation for ligation of the ductus, although he himself had never performed one on the living. He stated, in general, "The one cardiac valvular lesion which is relatively speaking superficial" could be attacked "by a short surgical route"; the ductus "could easily be surrounded with ligature." He "doubted whether it would materially hasten a fatal issue in case the diagnosis were not confirmed." The operation was advised for failure of the circulation.

Not until thirty-one years later was the first attempt to ligate the patent ductus arteriosus reported (Graybiel, Strieder and Boyer).[2] Their patient had superimposed subacute bacterial endarteritis. The purpose of the operation was to destroy the bacterial vegetation by obliteration of the ductus. An anterior mediastinotomy was performed. The ductus was plicated. They were unable to obliterate the lumen completely. The patient succumbed on the fourth postoperative day of acute dilatation of the stomach.

The first successful ligation of the patent ductus arteriosus was reported by Gross and Hubbard[3] in 1939. Their patient was a 7½ year old girl with uncomplicated patent ductus arteriosus. The indications for operation were beginning embarrassment of the circulation and hope of prevention of subacute bacterial endarteritis. The operation was a transpleural one, carefully and skilfully worked out by Dr. Gross.

The first recovery from subacute bacterial endarteritis on patent ductus arteriosus effected by surgical obliteration of the ductus was

From the Medical and Surgical Services of Beth Israel Hospital.

1. Munro, J. C.: Ligation of the Ductus Arteriosus, Ann. Surg. **46**:335, 1907.

2. Graybiel, A.; Strieder, J. W., and Boyer, N.: An Attempt to Obliterate the Patent Ductus Arteriosus in a Patient with Subacute Bacterial Endoarteritis, Am. Heart J. **15**:621 (May) 1938.

3. Gross, R. E., and Hubbard, J. P.: Surgical Ligation of a Patent Ductus Arteriosus, J. A. M. A. **112**:729 (Feb. 25) 1939.

reported by Touroff and Vesell in 1940.[4] Those reporting operations on uncomplicated patent ductus arteriosus at that time considered the presence of subacute bacterial endarteritis a contraindication to operation. The danger of increased bacteremia and embolization was mentioned. Ligation of the ductus in the case was proposed by one of us (H. V.) with the idea simply that it would eliminate factors (forceful blood current through the ductus) which were favorable to the development and maintenance of the bacterial endarteritis. The operation, in which the technic of Gross was used, was followed by prompt subsidence of the bacterial infection.

During the five years which have elapsed since this report, endarteritis in the ductus arteriosus gradually came to be accepted as an indication for surgical obliteration of the patent ductus. The operation was performed by many surgeons both here and abroad. Results were most gratifying in that a condition which previously was almost 100 per cent fatal became curable in the majority of cases.

During the past few years it has been demonstrated that penicillin therapy is effectual in cases of subacute bacterial endocarditis, including those with underlying patent ductus arteriosus.[5] It is therefore timely to consider the indications for surgical measures in the light of the five years of experience with operation and recently with penicillin.

After it was demonstrated that ligation or excision of the ductus could terminate the superimposed bacterial endarteritis,[6] it was felt that all patients in whom the diagnosis was definitely established should be operated on promptly with two exceptions.[7]

These exceptions were, first, patients with important associated congenital cardiac anomalies for which the ductal shunt was a vital com-

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4. Touroff, A. S. W., and Vesell, H.: Subacute Streptococcus Viridans Endarteritis Complicating Patent Ductus Arteriosus, J. A. M. A. **115**:1270 (Oct. 12) 1940.

5. (*a*) Loewe, L.; Rosenblatt, P.; Greene, H. J., and Russell, M.: Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis, J. A. M. A. **124**:144 (Jan. 15) 1944. (*b*) Dawson, M. H., and Hobby, G. L.: The Clinical Use of Penicillin; Observations in One Hundred Cases, ibid. **124**:611 (March 4) 1944. (*c*) MacNeal, W. J.; Blevins, A., and Poindexter, C. A.: Clinical Arrest of Endocarditis Lenta by Penicillin, Am. Heart J. **28**:669 (Nov.) 1944. (*d*) Paullin, J. E., and McLaughlin, C. J.: The Treatment of Subacute Bacterial Endocarditis with Penicillin, Ann. Int. Med. **22**:475 (April) 1945. (*e*) Spink, W. W., and Hall, W. H.: Penicillin Therapy at the University of Minnesota Hospitals: 1942-1944, ibid. **22**:510 (April) 1945.

6. Touroff, A. S. W.; Vesell, H., and Chasnoff, J.: Operative Cure of Subacute Streptococcus Viridans Endarteritis Superimposed on Patent Ductus Arteriosus: Report of the Second Successful Case, J. A. M. A. **118**:890 (March 14) 1942.

7. Touroff, A. S. W., and Vesell, H.: Experiences in the Surgical Treatment of Subacute Streptococcus Viridans Endarteritis Complicating Patent Ductus Arteriosus, J. Thoracic Surg. **10**:59 (Oct.) 1940.

pensatory mechanism and, second, patients with evidence of extension of bacterial vegetations beyond the ductus and pulmonary artery, particularly those with involvement of the left side of the heart. These exceptions will be considered later.

The establishment of the correct diagnosis naturally was a prerequisite to operation. That this was accomplished with little error is revealed in the fact that in 140 operations on the ductus (33 with subacute bacterial endarteritis) reviewed recently by Shapiro and Keys,[8] the diagnosis was in error in only 2. This group consisted only of cases in which operation for ductal closure had been performed. Data are not available concerning the uncertainty and inaccuracy of diagnosis in the large number of cases without operation.

Many observations contribute to the diagnosis of patent ductus arteriosus and subacute bacterial endarteritis. The usual history is that the patient was not a "blue baby." The presence of a cardiac murmur from infancy was almost always known. Cyanosis did not occur except with pulmonary or cardiac complications.

The most helpful diagnostic sign was the characteristic train-in-a-tunnel machinery murmur. Heard best just left of the sternum between the second and third intercostal spaces, it is loud, low pitched, rumbling and harsh. It grows louder during systole, reaching its maximum intensity in late systole and early diastole, and continues through most of diastole. A short silent period may be recorded in the phonocardiogram just before the first sound. When once heard the murmur can hardly be mistaken. The transmission of this murmur is quite uniform. The systolic component is well transmitted over most of the front and back of the chest, left and right; the interscapular transmission was described long ago by François-Franck.[9] The murmur can be heard in the left axilla and in the neck. The diastolic component, and consequently the continuous murmur as a whole, my colleague and I have found quite regularly to have a characteristic area of transmission, in the shape of a rectangle (fig. 1) with the following borders: upper, left clavicle; lower, fourth intercostal space; right, midsternum; left, the midclavicular line. The striking difference in size of the small area of transmission of the diastolic component from the very much larger area for the systolic is suggestive of a different source or origin for each component. Laubry and Pezzi[10] developed

8. Shapiro, M. J., and Keys, A.: The Prognosis of Untreated Patent Ductus Arteriosus and the Results of Surgical Intervention: A Clinical Series of Fifty Cases and an Analysis of One Hundred and Thrity-Nine Operations, Am. J. M. Sc. **206**:174 (Aug.) 1943.

9. François-Franck, M.: Sur le diagnostic de la persistance du canal artériel, Gaz. hebd. de méd. **25**:588, 1878.

10. Laubry, C., and Pezzi, C.: Traité des maladies congenitales du cœur, Paris, J. B. Ballière et fils, 1921.

some evidence to indicate that the diastolic component was produced by pulmonary insufficiency, while the systolic was produced in the ductus. There have been many explanations for the murmur. Some cases of patent ductus arteriosus even beyond childhood will undoubtedly be missed and patients deprived of the benefits of operation if, as recently suggested, the diagnosis not be made without the presence of a continuous machinery murmur. In some instances the murmur

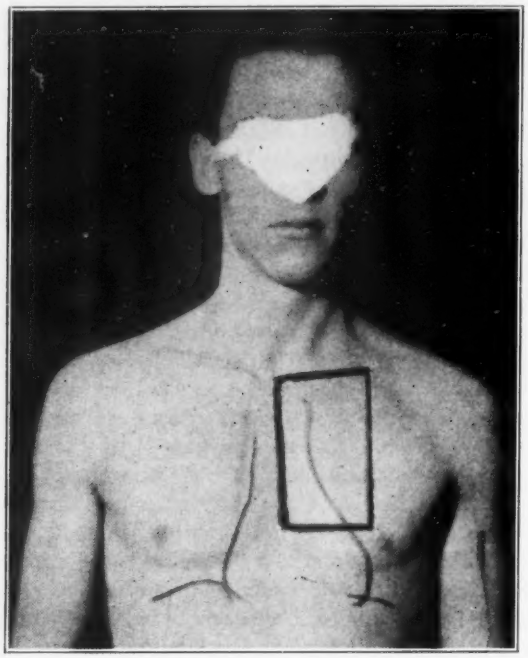

Fig. 1.—Rectangular area of transmission for the diastolic component of the continuous murmur of patent ductus arteriosus. (The subject with the outline of a normal heart on the chest is from Roesler, "Clinical Roentgenology of the Cardiovascular System." The illustration is reproduced by permission of Charles C Thomas, Publisher, Springfield, Illinois.)

is limited to systole. Abbott [11] found this to be so in 30 per cent of her 92 cases. It is not so common in adults. In 1 of our adult patients in whom this was the only murmur consistently heard, operation revealed a very short but wide ductus. The systolic was also the

11. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936, p. 32.

only murmur heard in 2 adults with uncomplicated patent ductus arteriosus. Rarely, a murmur is lacking.[12]

A thrill can almost always be felt over the area of the pulmonic valve; it may be brought out by having the patient bend forward and hold the breath in deep expiration.

The roentgenogram is frequently helpful in diagnosis, especially for those cases in which the labeling continuous murmur is lacking. The prominence of the pulmonary artery (roentgen ray cap of Zinn), with increased hilar and pulmonary markings (together referred to as Assmann's sign), occurs in over one half the cases. On fluoroscopy increased pulsation of the pulmonary artery was noted and considered of diagnostic value long ago by Wessler and Bass,[13] who also pointed out that, in contrast, the prominent pulmonary artery in mitral stenosis pulsates little. The roentgenokymogram reveals the great amplitude of the waves produced by the increased pulsations of the pulmonary artery (fig. 3), also some increase in the excursion of the left ventricular border.

Angiocardiography can be of considerable value in diagnosis. A characteristic and possibly pathognomonic abnormality has been pointed out by Sussman, Grishman and Steinberg.[14] In the left oblique position a small but definite bulge was found in the aortic shadow at the site of the aortic infundibulum of the ductus. This bulge occurred in 26 of their 27 cases. The size of the cardiac chambers may be normal. Angiocardiography should be employed in all doubtful cases, particularly those in which operation is contemplated.

The electrocardiogram is usually normal and is sometimes helpful in establishing the diagnosis by ruling out other conditions in which diagnostic changes are expected. There may be slight or moderate left axis deviation. Slight right axis deviation is infrequent and was seen only once in about 15 cases. Pronounced right axis deviation is strong evidence against the presence of patent ductus arteriosus as an isolated or primary defect.

The arterial blood pressure is altered rather characteristically in most cases. The diastolic pressure in the brachial artery is commonly about 20 to 30 mm. of mercury below normal, as in patients with a

12. (*a*) Goodman, E. H.: Report of a Case of Patent Ductus Arteriosus Botalli with a Study of the Cases Heretofore Published, Univ. Pennsylvania M. Bull. **23**:509 (Dec.) 1910-1911. (*b*) Shapiro, M. J.; Keys, A., and Violante, A.: Clinical and Physiological Analysis of Twenty-Three Patients with Persistent Patent Ductus Arteriosus, Internat. Clin. **4**:148 (Dec.) 1941.

13. Wessler, H., and Bass, M. H.: Persistent Ductus Botalli and Its Diagnosis by the Orthodiagraph, Am. J. M. Sc. **145**:543 (April) 1913.

14. Sussman, M. L.; Grishman, A., and Steinberg, M. F.: Newer Concepts in the Diagnosis of Congenital Heart Disease, Am. J. Dis. Child. **65**:922-936 (June) 1943.

large arteriovenous aneurysm. The systolic pressure is normal, usually a low normal. Typical blood pressures are systolic, from 100 to 125 and diastolic, from 45 to 60 mm. of mercury.

Bohn [15] has called attention to a response of the arterial blood pressure to exercise which he believed diagnostic. A control reading of the blood pressure is taken with the patient standing. The blood pressure cuff is left on the arm, and the patient exercises by taking ten knee bends (or their equivalent). A pressure reading is made immediately after. The diagnostic sign is the occurrence of a substantial reduction of the diastolic pressure following exercise. Elevation of the systolic pressure is noted as in normal subjects. Bohn warned that if more than a minute elapsed after the exercise is completed the characteristic response may be missed. In 1 of his patients, a 17 year old girl with patent ductus arteriosus and without cardiac decompensation, the resting blood pressure was 130 mm. of mercury systolic and 60 mm. diastolic; immediately after ten knee bends it became 200 systolic and 20 diastolic; then 165 systolic and 50 diastolic and 135 systolic and 50 diastolic, and, one minute after, 120 systolic and 60 diastolic. Aortic insufficiency, severe hyperthyroid heart and cardiac effects of high fever should be excluded. Bohn found the sign of considerable aid in the diagnosis of patent ductus arteriosus. Lewicki [16] has also found the sign of aid and has modified it slightly by adding a second series of ten knee bends to the exercise. In an 18 year old patient with patent ductus arteriosus and questionable cardiac decompensation he obtained the following blood pressure changes: control, blood pressure in the arm, 125 mm. of mercury systolic and 50 diastolic; after 10 knee bends, 165 systolic and 0 diastolic, and after ten more, 205 systolic and 0 diastolic. The blood pressures in the legs (tibialis posticus) were: control, 162 systolic and 90 diastolic; after ten knee bends, 173 systolic and 110 diastolic, and after ten more, 175 systolic and 110 diastolic. The diastolic pressure in the legs was raised rather than lowered after the exercise.

In our attempt to apply the test of Bohn, definite positive responses were obtained in several patients with uncomplicated patent ductus arteriosus. In the patients with endarteritis the test was not as satisfactory. Because of the inability of the patient to perform the regular test exercise other physical effort, allowing the patient to remain in bed, was substituted. Kicking back and forth against resistance and alternate sitting up and lying down were tried to the point of some fatigue of the patient. Little reduction in the diastolic pressure after

15. Bohn, H.: Ein wichtiges diagnostisches Phänomen zur Erkennung des offenen ductus art. Botalli, Klin. Wchnschr. **17**:907 (June 25) 1938.

16. Lewicki, E.: Zur Diagnostik des offenen Ductus arteriosus Botalli, Wien. klin. Wchnschr. **50**:1029 (Dec. 13) 1940.

the physical effort occurred: 122 mm. of mercury systolic and 46 diastolic before exercise and 144 systolic and 38 diastolic after; and 84 systolic and 48 diastolic before exercise and 90 systolic and 45 diastolic after, in 2 patients with ductal endarteritis in whose cases the diagnosis was confirmed at operation.

The test may be useful in the differential diagnosis of patent ductus arteriosus from other congenital (or acquired) cardiac lesions. In a patient with an interatrial septal defect, corroborated by angiocardiography, a negative response was recorded: when the patient was standing, blood pressure in the arm was 120 mm. of mercury systolic and 80 diastolic; after fifteen [17] knee bends, 140 systolic and 90 diastolic; at another time, when the patient was standing the pressure was 120 systolic and 70 diastolic; after fifteen knee bends, 124 systolic and 70 diastolic, and after fifteen more, 144 systolic and 70 diastolic. This suggests that a pronounced positive response with lowering of the diastolic blood pressure to close to zero, as often occurs after the second series of knee bends in patients with patent ductus arteriosus, should favor the diagnosis of patent ductus arteriosus against that of interatrial septal defect, in situations in which the two conditions are considered. This differential diagnosis is at times difficult, and any aid is desirable.

One adult with an interventricular septal defect, a diagnosis corroborated by angiocardiography, had the following response to the test exercise: the blood pressure, standing position, was 122 systolic and 84 diastolic; after ten knee bends it was 130 systolic and 70 diastolic, and after ten more, 132 systolic and 60 diastolic. A slightly positive reaction to the test would not be of value in the differential diagnosis of these two conditions. A strongly positive reaction to the Bohn test with reduction of the diastolic pressure to near zero would favor the diagnosis of patent ductus arteriosus.

On the basis of some or all of the mentioned clinical and laboratory features—history, murmur, reaction of blood pressure, together with the roentgenogram, roentgenokymogram and angiocardiogram—the diagnosis of patent ductus arteriosus should be made correctly in practically all cases.

The diagnosis of the superimposed subacute bacterial endarteritis was made on clinical and laboratory observations similar to those in cases with underlying acquired heart disease. Unexplained fever of one week or more in patients with patent ductus arteriosus requires that such a diagnosis be carefully considered or be made tentatively. Symptoms encountered early were irritability, weakness, anorexia, feeling of warmth with perspiration, chills, cough and loss of weight.

17. Fifteen instead of ten knee bends were used for more agile or robust young adults.

Recent dental extractions and pregnancy were occasionally associated and possibly connected. Petechiae were not common early. Systemic embolization occurred much later than in the ordinary subacute bacterial endocarditis. Pulmonary embolization was more frequent. Red blood cells were found in the urine infrequently. The blood culture contained the organism early and at times contained 100 to 400 colonies per cubic centimeter of blood. Finally, repeated blood cultures of the organism should be obtained for corroboration of the diagnosis of subacute bacterial endarteritis.

When the diagnosis of patent ductus arteriosus with subacute bacterial endarteritis was established, the possible presence of contraindications to operation had to be determined. There were two contraindications of importance. The first was associated congenital cardiac anomalies for which the patent ductus arteriosus was a vital compensatory mechanism. Experience has shown that such associated anomalies are most uncommon after infancy and if present would be expected to be revealed in cyanosis from associated pulmonary stenosis, and the signs of coarctation of the aorta—aortic stenosis or atresia if one of these conditions were also present. Fortunately such associated lesions were not noted in our experience and were extremely rare in the cases of others when operation was performed. Septal defects, atrial or ventricular, need not be a contraindication to the operation.

The second contraindication for operation is extension of infection beyond the ductus and especially to the left side of the heart. It has been argued that operation on the ductus could have no effect on bacterial vegetations in the aorta, in the mitral or aortic valves and probably not even on vegetations in the pulmonary valve. This conclusion cannot be wholly accepted, for it is far from proved. If it is true, the high percentage of cures by operation would be difficult to explain. Early reports based on necropsies in cases of patent ductus arteriosus with subacute bacterial endarteritis revealed that the infection, though starting at the pulmonic orifice of the ductus, had spread considerably beyond the ductus in most cases. Review of the first 19 reported cases (Schlaepfer 1926) [18] disclosed only 3 in which the bacterial infection was limited to the pulmonary artery and ductus; in the remaining 16 there was involvement of the valves: mitral alone, 5; aortic, 13 (9 with mitral); tricuspid, 1 (with mitral and aortic), and pulmonic valve, 9. Blumer and McAlenney [19] in 1931 reviewed 28 cases, and found the following involvement of valves: aortic valve, in 14 cases; pulmonary

18. Schlaepfer, K.: Chronic and Acute Arteritis of Pulmonary Artery and of Patent Ductus Arteriosus, Arch. Int. Med. **37**:473 (April) 1926.

19. Blumer, G., and McAlenney, P.: Relationship of Patent Ductus Arteriosus to Infectious Processes in the Duct Itself, in the Pulmonary Artery, the Aorta and the Heart Valves, Yale J. Biol. & Med. **3**:483 (July) 1931.

valve, in 14 cases; mitral valve, in 9 cases; tricuspid valve, in 4 cases, and multiple valves in 40.7 per cent of the cases. Gordon and Perla,[20] also writing in 1931, stated that up to that time there were only 4 recorded instances of patent ductus arteriosus with subacute bacterial endarteritis in which the valves were spared, and they added the fifth. Abbott [21] stated that in her collected series of 92 cases of primary patent ductus arteriosus there were 27 with mycotic endarteritis, in 23 (85 per cent) of which there was involvement of the valves of the heart and in only 4 (15 per cent) there was not. Hubbard, Emerson and Green,[22] in a review of 39 cases reported up to 1939, noted only 14 (35 per cent) without valvular involvement. If extension of the infection to the valves would destroy the chances of cure by ductal ligation, then, on the basis of the cited necropsy statistics, recovery should not occur in 65 to 85 per cent of the cases. This, however, was not borne out in the series of cases in which operation was performed. Of the 28 patients who survived operation 20, or 72 per cent, recovered.[8] Were the valves involved in 65 to 85 per cent of the cases in the necropsy series and in only 28 per cent of the patients operated on? In the series in which operation was performed the duration of the endarteritis was generally shorter, and therefore less extension of the bacterial vegetations would be expected. Observations on 3 patients who died at operation or shortly thereafter did show less extension. In 1 patient who died at operation [7] a few pinpoint verrucae were found on the pulmonary valve in addition to the vegetations in the ductus and pulmonary artery. In the 2 others there was no involvement of the valves. One [2] of these patients died four days after operation; vegetations were found in the pulmonary artery 1 cm. above the right leaflet of the pulmonary valve. In the third [7] case the patient died at operation. The ductus was destroyed at operation. Two firm vegetations, each about 3/16 inch (0.48 cm.) in diameter, were found in the pulmonary artery immediately opposite the opening of the ductus. The duration of the endarteritis prior to operation in these 3 patients was three and one-half months, four months and five months. The difference in duration of bacterial infection between the series with operation and the necropsy series undoubtedly accounts for freedom of the valves from infection in many of the former. However, because of the high

20. Gordon, H., and Perla, D.: Subacute Bacterial Endarteritis of the Pulmonary Artery Associated with Patent Ductus Arteriosus and Pulmonic Stenosis, Am. J. Dis. Child. **41**:98 (Jan.) 1931.

21. Abbott, M., in Nelson's Loose-Leaf Medicine, New York, Thos. Nelson & Sons, 1942, vol. 4, p. 269.

22. Hubbard, J. P.; Emerson, P., and Green, H.: Indications for the Surgical Ligation of a Patent Ductus Arteriosus, New England J. Med. **221**:481 (Sept. 28) 1939.

incidence (65 to 85 per cent) of valve involvement in the cases in which there was necropsy it seems likely that in some of the 20 (72 per cent) patients who recovered after operation the valves too were involved. In support of this inference is the long duration of infection (seven to ten months) in several patients operated on successfully, and also the short period of time after onset of infection that valvular involvement may occur—three and a half months in the first of the 3 cases just cited. The presence of signs of embolization in the systemic circuit in some of the surgically treated group also suggests that there were vegetations on the valves or in the aorta. Recovery even after involvement of the valves may be explained in the following manner. First, there is some natural tendency for vegetations on valves to heal. Pathologic specimens of infected valves in most cases of subacute bacterial endocarditis commonly show evidence of some degree of healing.[23] The occurrence of healing is also documented by the cases (1 to 3 per cent) of spontaneous recovery.[24] Second, in patent ductus arteriosus with subacute bacterial endarteritis bacterial infection of the valve develops on a normal valve instead of one with underlying rheumatic or other disease. Healing should be less difficult. Ordinarily subacute bacterial endocarditis rarely develops on normal valves. The third and most important reason for healing of the valvular infection is the elimination of the current through the ductus and infection in it by the surgical procedure. Thus a feeding source for other sites (valves) of cardiac infection is eradicated. A forceful blood current with strong eddies and turbulence appears to be necessary for the development and maintenance of bacterial vegetations in the heart or in arteriovenous aneurysms with subacute infection with Streptococcus viridans. The forceful currents and eddies favor the production of fibrin necessary for the protection of the bacterial growth, so that bactericidal polymorphonuclear leukocytes[25] may not reach and destroy the bacteria. It is meaningful that subacute bacterial endocarditis is common in mitral insufficiency, aortic insufficiency, patent ductus arteriosus and ventricular septal defects, but uncommon in tight mitral stenosis or in atrial septal defects. The presence of forceful blood currents and eddies produced by strong ventricular contraction in the former may be the reason. Elimination of the forceful whirling current of the ductus by operation is curative at least in part through this mechanism.

23. Libman, E.: A study of the Endocardial Lesions of Subacute Bacterial Endocarditis with Particular Reference to Healing or Healed Lesions, Am. J. M. Sc. **144**:313 (Nov.) 1912.

24. Libman, E., and Friedberg, C. K.: Subacute Bacterial Endocarditis, New York, Oxford University Press, 1941, p. 81.

25. Friedman, M.; Katz, L. N., and Howell, K.: Experimental Endocarditis Due to Streptococcus Viridans, Arch. Int. Med. **61**:95 (Jan.) 1938.

The presence of petechiae has been considered a contraindication to operation. There are two important reasons that this need not be so. First, petechiae may be purpuric or may be due to a toxic endotheliitis rather than to bacterial embolization.[24] Second, in some cases in which they are caused by bacterial emboli, the bacteria may have had their source in the vegetations in the ductus and may have been forced through the dilated pulmonary vascular bed by the increased pulmonary vascular pressure to reach the systemic circulation. Even should they be derived from valvular vegetations recovery could still be possible, as a result of the obliteration of the ductus. Besides the better chance for a normal valve to heal there would be the added benefit from a potent chemotherapy now available on a lesion rendered less formidable after obliteration of the ductus. Petechiae or other evidence of systemic embolization and left-sided cardiac involvement therefore should not constitute an absolute contraindication to operation.

There is no longer any doubt that penicillin is curative of the bacterial infection in many cases of subacute endocarditis caused by S. viridans. Loewe, Dawson, MacNeal, Paullin, Spink[5] and others have adequately demonstrated this. Subacute bacterial endarteritis with patent ductus arteriosus has responded at least as well as with other complications (Spink).[5e] The percentage of cure is somewhat over 50 and probably higher with larger dosage. The problem in endarteritis with patent ductus arteriosus is whether penicillin without operation should be the treatment of choice or whether operation should be performed also, and if so when.

There are three circumstances in which operation is indicated. First, operation is indicated in cases in which the bacteria obtained on blood culture were found by test in vitro to be insensitive to penicillin; organisms in this category would include gram-negative bacilli, most higher bacteria and some strains of alpha hemolytic streptococcus which are resistant to concentrations of penicillin obtainable in the blood stream. Greater availability of the drug now permits the development of high concentrations in the blood and should substantially reduce the number of the last group. Thirty million units per day have been administered, and, a concentration of 60 Oxford units per cubic centimeter of blood reached.[26]

Second, operation is indicated for those patients in whom the bacterial infection has been going on for a rather long time. Just how long the time limit should be would be arbitrary. About three months should be a suitable time, but this would depend in large part on the condition of the patient. This second group would include cases in which the bacteria present are sensitive to penicillin;

26. Loewe, L.: Personal communication to the author.

these patients would also receive penicillin. Reasons for prompt operation in these patients would be to avoid extension of the bacterial invasion to other parts of the heart, particularly to the left side of the heart, the mitral and aortic valves, where eradication of the infection would be more difficult. With delay too, the possibility of serious unpredictable complications becomes greater. Cerebral, visceral and peripheral embolization occurs without warning, at almost any time, and all these complications are serious and frequently fatal. Also of considerable importance is the increase in inflammation in and around the ductus with resultant increase in friability and with firm adhesions of the tissues as the infection is prolonged. If chemotherapy, which would take additional time—possibly weeks—should prove unsuccessful, then because of the delay greater danger of hemorrhage would be placed on the operation than necessary.

A third type of case which requires surgical treatment is the following: The bacterial organism is sensitive to penicillin, but for various reasons, after a trial period of several weeks, the response to treatment is not satisfactory. There may be an initial clearance of the blood stream and disappearance of symptoms and signs, but relapse takes place shortly. Relapse may be only in the form of a return of the positive blood culture, with little or no fever. Such a case is the one reported later in this article. In that case the imminence of cardiac failure, which in itself is an indication for obliteration of the patent ductus, made the decision to operate less difficult. The imminence or presence of cardiac failure in any case of patent ductus arteriosus with subacute bacterial endarteritis favors the decision to operate promptly so that the operation necessary for correction of the circulatory defect may also be curative of the endarteritis. Penicillin, of course, should be administered simultaneously in cases in which the bacteria are sensitive.

The following three considerations should be carefully weighed when the surgical treatment is proposed. The first is the operative mortality. In the hands of a patient and capable surgeon of the chest this may not be much more than for operation on the noninfected ductus, if performed early in the course of the infection. The operative mortality is about 8.5 per cent for uncomplicated cases and 15 per cent for those with subacute bacterial endarteritis [12a]; it is less with greater experience and an improvement in technic. The second is that life expectancy in patients with patent ductus arteriosus even without infection is considerably below normal without operation. The average age of the patients in Abbott's series of fatal cases was only 24 years. Though this would be higher if living patients were properly included and infants excluded, it would still be much below normal. The third is the benefits and length of life attained

after operation. This of course remains to be determined. The first patient with subacute bacterial endarteritis cured by the surgical treatment [4] is still well and at regular work five years after the operation. Another patient with the same condition [6] is well and at regular work four years after the operation.

REPORT OF A CASE

History.—F. S., a native-born white woman aged 25 years, single, a secretary, was admitted to the medical service of Beth Israel Hospital Jan. 22, 1945. One of three children, she was not a "blue baby." A cardiac murmur was first noted at the age of 2 years. At school, high school and college she indulged in activities requiring ordinary physical effort, such as stair climbing, without undue fatigue or breathlessness. However, she was advised to abstain, and did, from games involving strenuous physical effort. She was always physically well developed and well nourished.

About two years before admission she had influenza; then for four weeks she received digitalis medication for supposed cardiac failure. For the two years following this attack of influenza she did not feel well, becoming more easily fatigued and short of breath on less effort. Three weeks prior to admission she became ill with a sore throat, swelling of the cervical lymph nodes and fever. Infectious mononucleosis was suspected, and a course of sulfonamide therapy was given. She began to lose weight; the fever persisted, and she was then sent to the hospital.

Examination.—The patient was well developed, well nourished, and weighed 120 pounds (54.4 Kg.). She did not appear acutely ill. The temperature was 102.6 F., the pulse rate 130, and the respiratory rate 26 per minute. There was no dyspnea or cyanosis. Petechiae were not seen on the conjunctivas, throat, trunk or extremities. Several cervical lymph nodes posteriorly were moderately enlarged and tender. Teeth were not visibly carious. A slight postnasal drip was present. Prominent pulsations were visible in the vessels of the neck near the clavicle. A systolic thrill was felt in the jugulum. The heart appeared to be slightly enlarged. A rather forceful apex impulse was palpable just outside the midclavicular line in the fifth intercostal space. Here the first sound was moderately loud, accompanied and followed by a systolic murmur of 2 plus intensity (6 plus maximum); the second sound was slightly accentuated. Over the second intercostal space just left of the sternum there was a systolic impulse, of moderate force, and a purring thrill which occupied most of systole and diastole. Over this area a continuous, loud, machinery murmur was heard—intensity 4 to 5 plus. The systolic component was well transmitted to the apex, the aortic area, the right and left interscapular areas, the bases of both lungs and the neck on both sides. The diastolic component was heard well only in the rectangular area described in figure 1: above to the clavicle, below to the fourth intercostal space, to the midsternum on the right and to the midclavicular line on the left. The pulmonic second sound was slightly accentuated, the aortic second normal. There was no evidence of cardiac failure. Circulation time, measured with sodium dehydrocholate, was twelve seconds, and venous pressure was 95 mm. of water. The lungs were clear; the liver was not palpable; the spleen was felt 1 to 2 fingers below the costal margin. There was no clubbing of the fingers. The blood pressure in the standing position was 116 mm. of mercury systolic and 46 diastolic; after ten feeble knee bends it was 118 systolic and 30 diastolic, and after ten more 116 systolic and 24 diastolic. Four weeks later blood

pressure in the standing position was 144 systolic and 70 diastolic, and after ten knee bends 150 systolic and 24 diastolic; leg pressure (at knee) was 200 systolic and 126 diastolic; after ten knee bends it was 250 systolic and 140 diastolic.

Laboratory Data.—A teleroentgenogram revealed the heart to be a little enlarged in the region of the left ventricle. There was slight prominence of the pulmonary artery arc with straightening of the left cardiac border (fig. 2), and moderate increase in hilar and peribronchial markings. Kymographic examination showed wide pulsations of the pulmonary artery (fig. 3). The electrocardiogram revealed a left axis deviation. The R wave in lead I was high, 21 mm.; the R wave in lead II was 3 mm.; the S wave in lead III was 13 mm., and the angle alpha was plus 8 degrees; T waves were erect. The chest lead, IV F, was normal. A

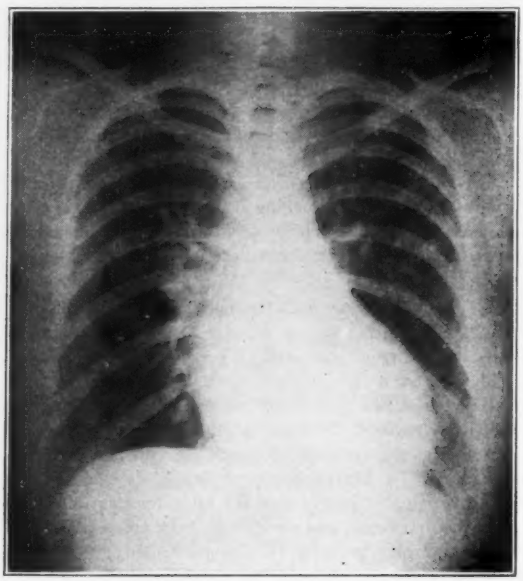

Fig. 2.—Teleroentgenogram showing slight prominence of pulmonary artery, some increase in size of the left ventricle and increase in hilar and peribronchial markings.

phonocardiogram (fig. 4) revealed a continuous murmur over the pulmonic area. There was a short silent period just before the first sound. The specific gravity of the urine was 1.020; reactions to tests for albumin and dextrose were negative. An occasional red blood cell was seen in the low power field. No casts were found. The blood contained 4,150,000 red cells per cubic millimeter; hemoglobin content was 11.5 Gm. per hundred cubic centimeters of blood. There were 12,000 white cells, of which 76 per cent were polymorphonuclear leukocytes, including 7 per cent "staff" cells; 20 per cent were lymphocytes, 4 per cent large mononuclear cells. The erythrocyte sedimentation rate was 50 mm. in one hour. Reactions to the Wassermann, Kline and Kahn tests were negative. The heterophile antibody reaction was negative on admission and also twenty days later. A blood culture

taken the morning after admission revealed 82 colonies of alpha hemolytic streptococcus or S. viridans per cubic centimeter of blood. The following day, January 24, another blood culture was taken, and 150 colonies per cubic centimeter grew out.

The diagnosis of patent ductus arteriosus with complicating subacute bacterial (S. viridans) endarteritis was made. Because of the good general condition of the patient, good nutrition, absence of signs of cardiac failure and the short duration of the infection, it was decided to treat the patient medically with penicillin rather than by immediate operation. The medical treatment was less formidable and, according to reports at the time, very hopeful. Tests in vitro revealed the

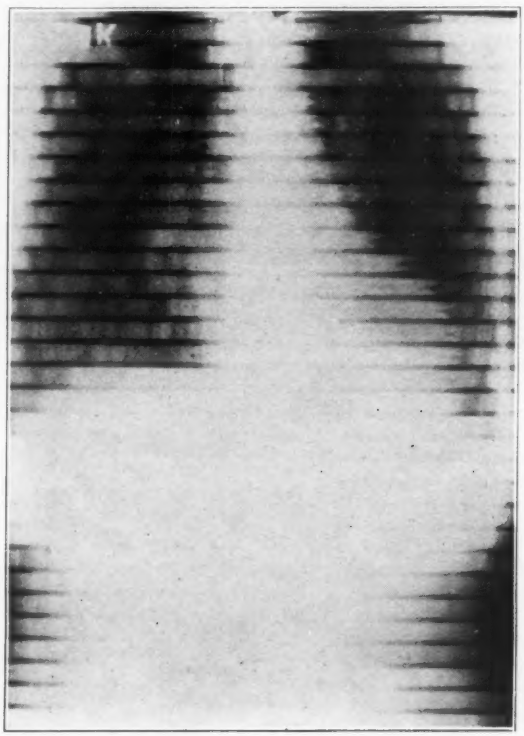

Fig. 3.—Roentgenokymogram showing some increase in pulsations of the pulmonary artery and left auricular region.

organism to be sensitive to as low a concentration as .0125 units of penicillin per cubic centimeter. If satisfactory results were not obtained in about two weeks, operation on the ductus was contemplated. The treatment was started on January 24, with 40,000 units intravenously and a continuous intramuscular infusion. After ten hours the continuous intramuscular infusion was stopped because of pain in the thigh at the site of injection. Eighty thousand units had been given by this route. Intermittent intramuscular administration was then started with 25,000 units every three hours, 200,000 units per day. The patients temperature returned to

normal the day after the penicillin was started and after only 120,000 units had been given. Her general condition improved, and she said that she felt much better. After three days of normal temperature the dosage of penicillin was reduced to 15,000 units and 10,000 units every three hours, alternately. This was

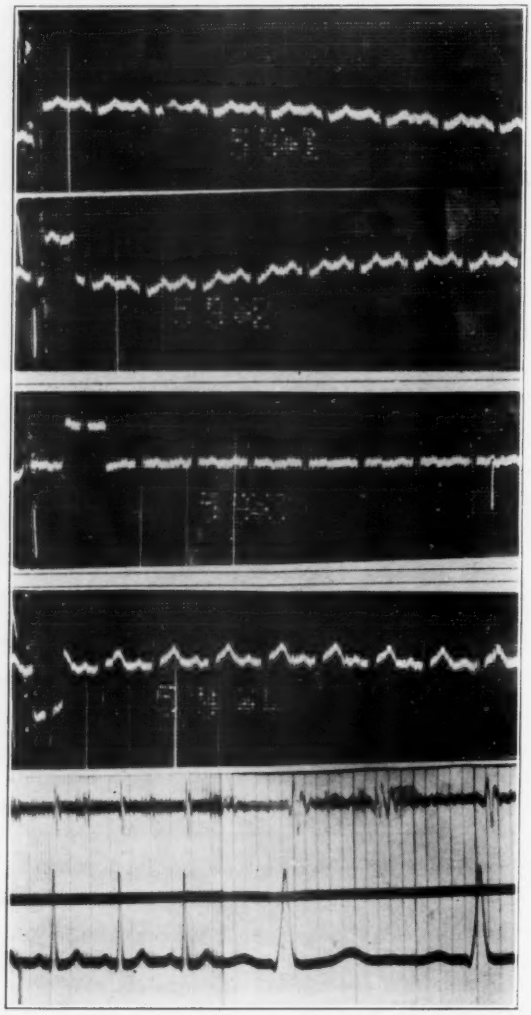

Fig. 4.—Electrocardiogram, leads I, II, III and CF_{IV}; left axis deviation, angle alpha plus 8 degrees. Phonocardiogram with lead I of the electrocardiogram at the bottom; vibrations due to the continuous murmur occupy all of systole and diastole with a short silent period before the first sound.

done to conserve the penicillin, the supply at hand having become low. A blood culture January 29, five days after the beginning of treatment, was also sterile. The temperature remained under 100 F. for eleven days, when another blood culture was taken and was reported to contain the organism, 2 colonies per cubic centimeter. The dosage of penicillin was then increased to 20,000 units every three hours for two days through February 9, then to 25,000 units intramuscularly every three hours—200,000 units every twenty-four hours. The temperature rose to between 100 F. and 101 F. daily. The patient began to feel ill again. A blood culture on February 12 revealed 12 colonies per cubic centimeter of blood. It was now quite uncertain whether the penicillin therapy would be successful in clearing the infection, at least in the dosage in which the drug was available for treatment. The blood concentration of penicillin on one determination three hours after injection was less than 0.02 unit per cubic centimeter. It was now three and a half weeks since the beginning of treatment and six and a half weeks since the onset of the infection. It was considered advisable not to delay operation for the following reasons: the uncertainty of cure by penicillin alone; the possibility of extension of bacterial vegetations to the valves, especially on the left side of

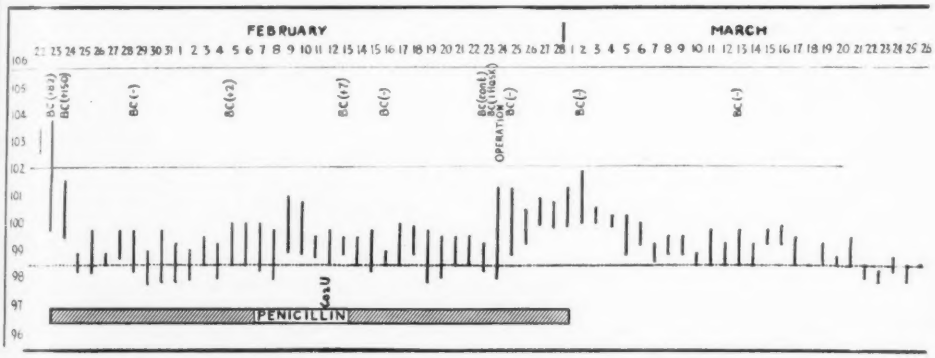

Fig. 5.—Clinical course of F. S. in the hospital. *B. C.* = blood culture; *U* = Oxford units of penicillin.

the heart; the possibility of increasing inflammatory changes in and about the ductus with resultant increased friability of tissues and formation of adhesions making operation more hazardous; the possibility of sudden, unpredictable serious embolization to the brain, viscera or extremities, all of which is more likely to happen as the infection is prolonged. Ligation of the ductus had been shown in the past to produce prompt and permanent clearance of the infection of the blood stream.

Additional indication for obliteration of the ductus was the fact that the patient's circulatory status was threatened by the defect. This was expressed in the increasing shortness of breath the patient had been experiencing during the past two years. Impending cardiac failure being an indication for operation, it was felt that operation might be carried out promptly and so take care of the infection as well as of the circulatory defect.

Accordingly the operation on the ductus was performed on Feb. 24, 1945, by Dr. I. Kross. The posterior lateral approach was chosen for the reasons

mentioned by Dr. Stuart Harrington,[27] who first employed it. The anesthetics cyclopropane and ether were administered by tracheal airway after morphine and atropine had been given hypodermically. The pleural cavity was entered through the bed of the fourth rib. The lung was collapsed and the mediastinal pleura incised longitudinally over the aorta and the pulmonary artery between the phrenic and vagus nerves, exposing the arch of the aorta and the pulmonary artery. The areolar tissue was rather edematous and contained several blackish colored lymph nodes. The ductus was isolated by blunt dissection; all except the posterior surface had been freed when bleeding occurred. The ductus was then clamped, sutured and incised. The strong thrill completely disappeared. The edges of the mediastinal pleura were partially brought together with two interrupted catgut sutures; 5 Gm. of sulfanilamide powder was placed in the mediastinum before closing; an equal amount was placed in the pleural cavity before the chest was closed. The lungs were inflated and practically all the air in the pleural cavity expressed.

The postoperative reaction and shock were moderate. The patient received oxygen in a tent; carbon dioxide was given periodically for deep breathing. Blood and isotonic solution of sodium chloride were given, in reduced amounts because of the increased blood volume due to the circulatory shunt. The general systemic reaction and shock were about the same as in patients with whom the anterior approach was used. The machinery murmur completely disappeared. No cardiac murmurs were heard except for sounds of mediastinal emphysema and pericarditis for a few days. About twelve days after operation a short faint systolic murmur could be heard over the area of the pulmonary valve. The diastolic blood pressure rose to normal; the blood pressure was 120 systolic and 80 diastolic. The spleen was no longer palpable.

Penicillin therapy was continued for six days after operation to prevent postoperative infection. The temperature returned to normal after nine days, and it has remained so since. She was allowed out of bed on March 7.

In preoperative blood cultures taken February 5 and February 13 the organism was present. Those taken February 16 and one flask (plates contaminated) taken on February 24 just before operation, as well as all postoperative blood cultures, February 25, March 2, March 13 and March 27, were sterile. There was a complete return of her former sense of well-being, and she gained 4 pounds (1.8 Kg.). She was discharged March 30 to take about one month of rest before returning to work. Last seen on September 12, seven months after operation, she was in excellent condition and had been working regularly.

SUMMARY AND CONCLUSIONS

Indications for the surgical treatment of subacute bacterial endarteritis complicating patent ductus arteriosus were discussed. Correct diagnosis, a prerequisite to operation, and the following features in diagnosis were considered: the murmur, roentgenographic studies, the electrocardiogram and blood pressure tests.

Contraindications to operation considered were associated congenital cardiac anomalies and extension of the bacterial involvement to the left side of the heart. Petechiae and systemic embolization were not believed to be absolute contraindications.

27. Harrington, S.: Patent Ductus Arteriosus with Bacterial Endarteritis, Proc. Staff Meet., Mayo Clin. **18**:217 (July 14) 1943.

Penicillin therapy of subacute bacterial endarteritis with patent ductus arteriosus was discussed. Operation was believed indicated (1) when the bacteria causing the subacute bacterial endarteritis were insensitive to penicillin; (2) when infection was of long duration, and (3) when a trial with penicillin therapy was not completely successful and final cure was uncertain.

A case of the last type was described. In this case the patient was treated with penicillin and surgical measures with recovery.

PNEUMONIA IN THE AGED

An Analysis of One Hundred Sixty-Six Cases of Its Occurrence in Patients Sixty Years Old and Over

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IN THE forty-seven years that have elapsed since the publication of the third edition of Osler's famous textbook, one familiar paragraph has remained unchanged in all revisions. "Pneumonia may well be called the friend of the aged. Taken off by it in an acute, short, not often painful illness, the old escape those 'cold gradations of decay' that make the last stage of all so distressing." [1] Modern chemotherapy has made it necessary to revise this famous dictum. Today it is almost commonplace of clinical experience to see old persons recover from acute pulmonary infections, in spite of cardiovascular or pulmonary complications, when actively treated with agents such as the sulfonamide compounds and antibiotics such as penicillin, in conjunction with inhalation of oxygen and measures to combat the associated diseases.

In a disease in which the incidence has been reported as high as 2,000 per hundred thousand in persons over 70, compared with an incidence of 640 in the age group of 15 to 20 years,[2] accurate knowledge of its behavior in the aged is essential for the practitioner. Even today textbooks and medical journals contain such designations as "senile," "terminal" and "hypostatic" pneumonia, terms which imply that some cases of pneumonia are essentially due to old age, or to rest in bed, or to antecedent diseases, and not to active infection. Such terms not only are inaccurate but also imply an unjustified hopelessness and induce a feeling of defeatism in the physician. It must be realized that nearly all pneumonias in the aged are primarily infectious in origin, and that

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From the Medical Services of the Mount Sinai Hospital and the Home for Aged and Infirm Hebrews, New York.

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1. Osler, W.: The Principles and Practice of Medicine, ed. 15, New York, D. Appleton-Century Company, Inc., 1944. In the first edition (1892) and the second edition (1895) pneumonia is referred to as "the special enemy of old age." The quotation cited above occurs for the first time in the third edition (1898), where pneumonia is included with the specific infectious diseases instead of with the diseases of the respiratory system, as in the previous editions.

2. Heffron, R.: Pneumonia with Special Reference to Pneumococcus Lobar Pneumonia, New York, Commonwealth Fund, 1939.

the remainder are secondarily so involved. While in the young the presence of pneumonia is readily determined by the symptoms and signs, in the aged associated diseases or atypical features may often dominate the clinical picture and mask the involvement of the lung.

The factors which influence the occurrence and modification of pneumonia in the aged are the general and local changes associated with senescence as well as the high incidence of associated diseases. The local senescent changes include the relative fixation of the thoracic cage due to calcification of the costal cartilages, the loss of elasticity of the pulmonary tissues, the lessened motility of the bronchial cilia and the depression of the cough reflex. The general tissue changes associated with the aging process are gradual desiccation of the tissue, gradual retardation of cell division, diminished power of cell division and of tissue repair, retardation in the rate of tissue oxidation and cellular atrophy.[3] Immunologic changes have been emphasized by Kaufman.[4] The observation of the decline of the isoagglutinin titer in old age and the parallelism between this titer and the ability of the body to form bacterial antibodies led him to attempt to raise this titer and produce active immunization by the use of antigenic pneumococcus polysaccharides. While these measures seemed to lessen the incidence of the disease, there was no effect on the case mortality.

In an effort to clarify some of the problems presented by pneumonia in old persons, we have studied 166 consecutiive cases of pneumonia occurring in patients over 60 years of age from the wards of the Mount Sinai Hospital and the Home for Aged and Infirm Hebrews, covering the period of five and one-half years between Jan. 1, 1940, and June 30, 1945. In 143 of these, or 86 per cent, the clinical diagnosis of pneumonia was confirmed by roentgenologic examination, fluoroscopy or necropsy. One hundred and forty patients received sulfonamide drugs, 9 received penicillin and 2 were treated with both drugs. Four patients received type-specific serum in addition to sulfonamide drugs. The total number who died in the entire series was 33, or 20 per cent of the total. An analysis according to age, sex and outcome is shown in table 1, and according to causative organism and outcome in table 2.

ANALYSIS OF CASES ACCORDING TO AGE, SEX, OUTCOME AND CAUSATIVE ORGANISM

In table 1 there are 99 men with a mortality of 23 per cent, and 67 women with a rate of 15 per cent. These differences in incidence and outcome are to be considered along with the well known sex

3. Carlson, A. J.: Older Worker, Hygeia **21**:338-339 and 375-377 (May) 1943.
4. Kaufman, P.: Studies on Old Age Pneumonia, Arch. Int. Med. **67**:304-319 (Feb.) 1941.

differences of later life, such as the greater longevity, the lower incidence of arteriosclerotic heart disease and malignant neoplasms, and the greater mental stability of aged women. From this series of cases of pneumonia one is tempted to postulate an increased resistance to this type of infection in older women.

The greater number of the cases of pneumonia occurred in persons aged 60 to 75 years. Although the higher age brackets are less well represented, there is no correlation between age and mortality, since the highest rates occurred in men aged 65 to 69 years, and in women

TABLE 1.—*Analysis of One Hundred and Sixty-Six Cases According to Age, Sex and Outcome*

Age Groups	Male		Female	
	Cases	Deaths	Cases	Deaths
60-64	39	6	18	1
65-69	23	10	24	3
70-74	20	4	19	6
75-79	11	2	3	0
80 and over	6	1	3	0
Total	99	23	67	10 166
Death Rate	23 per Cent		14.9 per Cent	
Total Mortality 20 per Cent				

TABLE 2.—*Analysis of One Hundred and Sixty-Six Cases in Persons Sixty Years Old and Over According to Cause and Outcome*

	Total	Deaths	Mortality, Per Cent
A. Pneumonia due to specific organisms.			
1. Diplococcus pneumoniae	65	8	12
2. Streptococcus pyogenes	6	0	..
3. Staphylococcus aureus	1	0	..
4. Klebsiella pneumoniae	1	0	..
B. Pneumonia due to filtrable viruses.			
1. Primary atypical ("virus pneumonia")	12	0	..
2. Influenzal (epidemic) pneumonia	1	1	100
C. Suppurative bronchopneumonia (Neuhof)	7	5	70
D. Pneumonia of undetermined origin	73	19	24.6

aged 70 to 74 years. Of the 23 men and women 75 years old and over only 3 died, yielding a mortality rate of 13 per cent. These figures may be compared with those of Stahle,[5] who, in reporting on 15,000 cases of pneumonia with a gross fatality rate of 9.19 per cent, included 2,243 persons over 60 years of age, with a mortality rate of 23.99 per cent. These patients were treated with sulfonamide drugs either alone or in combination with specific serum.

In table 2 the series is broken down according to cause and outcome. In Group A, which includes pneumonias due to specific organisms,

5. Stahle, D. C.: A Clinical Analysis of Fifteen Thousand Cases of Pneumonia, J. A. M. A. **116**:440-447 (Feb. 7) 1942.

there are 65 cases due to various types of pneumococci, with 8 deaths, or a mortality rate of 12 per cent. The types, arranged according to frequency and fatality, are enumerated in table 3. Sixteen cases, or 25 per cent of the whole group of pneumococcic infections, were due to Pneumococcus type III; of these, 3 cases were fatal, or nearly 20 per cent. Type XX was found in 3 cases, all of which were fatal; 1 death each occurred from type VII and type VIII infections. Of interest in this connection is the report of Rumreich,[6] who in a nation-wide study of the causation of the pneumonias found that three quarters of all cases were due to pneumococci, and that three quarters of these were due to these types in the order named: I, III, VIII, VII, IV, V, XIV, II, VI and XIX. Although we had only 65 patients with pneumococcus pneumonia, and they were treated with sulfonamide drugs, serum and penicillin, the mortality rate of 12 per cent may be compared with the results of Kaufman,[7] who, using only sulfapyridine for 81 patients

TABLE 3.—*Incidence of Various Types of Pneumococci and Their Relation to Mortality*

Type	No. of Cases	Mortality	Type	No. of Cases	Mortality
I	5	0	XV	1	0
II	2	0	XVII	8	0
III	16	3	XIX	1	0
IV	10	0	XX	3	3
V	1	0	XXII	2	0
VII	4	1	XXIV	2	0
VIII	5	1	XXXI	1	0
IX	2	0	XXXII	1	0
XI	1	0	XXXIII	1	0
XIV	2	0	Untyped	3	0
			Total	65	12%

ranging from 50 years to 90 years, recorded a mortality rate of 23.5 per cent. Flippin, Schwartz and Domm[8] studied 1,635 proved cases of all types of pneumococcic pneumonia, occurring in patients of all ages, treated with sulfonamide drugs. The general mortality rate was 10.6 per cent; for patients under 50 years it was 5.7 per cent, while for patients over 50 years the rate was 21.9 per cent.

The cases of streptococcic and staphylococcic pneumonia in this series are too few in number to warrant any generalizations. In the study of the New York City Pneumonia Control Program, Lawrence and Sutliff[9] reported 8 cases of streptococcic pneumonia treated with

6. Rumreich, A. S., and others: A Nation-Wide Study of the Bacterial Etiology of the Pneumonias, Pub. Health Rep. **58**:121-135 (Jan. 22) 1943.

7. Kaufman, P.: Effect and Toxic Effect of Sulfapyridine in Old Age Pneumonia, New York State J. Med. **40**:204-208 (Feb. 1) 1940.

8. Flippin, H. F.; Schwartz, L., and Domm, A. H.: Modern Treatment of Pneumococcic Pneumonia, J. A. M. A. **121**:230-237 (Jan. 23) 1943.

9. Lawrence, E. A., and Sutliff, W. D.: Streptococcus Pneumonia, New York State J. Med. **40**:1233-1235 (Aug. 15) 1940.

sulfonamide drugs, with 2 deaths in patients over 60 years of age, as compared with a former general mortality rate at all ages of 35 to 60 per cent. Keefer, Rantz and Rammelkamp [10] stated that the hemolytic streptococcus causes 3 to 5 per cent of all cases of pneumonia, but that the frequency varies in epidemics. Of their 55 patients, 7 were over 60 years old, and of these 5 died. They emphasized the serious import of bacteremia and heart failure. Staphylococcic pneumonia, according to Gáspár [11] occurs in 75 per cent of the cases in which the patients are in the first decade of life, and is unusual when the patients are over 40 years of age.

Since only 1 case of pneumonia due to infection with Klebsiella pneumoniae is included in our series, attention is directed to the work of Baehr, Shwartzman and Greenspan,[12] who stress the frequency of this pathogen in the biliary and urinary tracts and in the perforative lesions of the abdomen, and its rarity in pneumonia. They deplore the misplaced emphasis of the scientific name of the organism. Small series of cases of pneumonia due to Bacillus Friedländer have been reported by Solomon [13] and by Perlman and Bullowa.[14] The latter emphasize that B. Friedländer pneumonia of the A type occurs predominantly in older persons. In 7 of 29 cases the patients were over 60 years of age, and the 7 cases were all fatal. In 8 cases of B. Friedländer pneumonia of the B type all the patients were under 60 years of age.

Group B of table 2 lists the pneumonias due to filtrable viruses. One case of hemorrhagic necrotizing pulmonary inflammation, characteristic of the fulminating influenzal infections seen in the 1918-1919 epidemic, had a fatal termination. In the primary atypical or "virus" [15] pneumonia group are included 12 cases, none of which were fatal. The benign course of this disease in the aged conforms to the experience

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10. Keefer, C. S.; Rantz, L. A., and Rammelkamp, C. H.: Hemolytic Streptococcal Pneumonia and Empyema: Study of Fifty-Five Cases with Special Reference to Treatment, Ann. Int. Med. **14**:1533-1550 (March) 1941.

11. Gáspár, I. A.: A Study of Primary Staphylococci Pneumonias Occurring at the Rochester General Hospital, New York State J. Med. **41**:834-840 (April 15) 1941.

12. Baehr, G.; Shwartzman, G., and Greenspan, E. B.: Bacillus Friedländer Infections, Ann. Int. Med. **10**:1788-1801 (June) 1937

13. Solomon, S.: Primary Friedländer Pneumonia: Report of Thirty-Two Cases, J. A. M. A. **108**:937-947 (March 20) 1937.

14. Perlman, E., and Bullowa, J. G. M.: Primary Bacillus Friedländer (Klebsiella Pneumoniae) Pneumonia, Arch. Int. Med. **67**:907-920 (May) 1941.

15. Reimann, H. A.: Viral Pneumonias, Bull. New York Acad. Med. **19**: 177-182 (March) 1943; Atypical Pneumonia, Viral Pneumonia or Viroid Pneumonia? Correspondence, J. A. M. A. **127**:543 (March 3) 1945.

in all age groups of other clinicians.[16] The diagnosis in our cases was based on the onset and clinical picture, the normal or low white blood cell count, the roentgenologic observations, the absence of pathogenic bacteria from the sputum and the lack of response to sulfonamide drugs. Flippin has warned against making the diagnosis too often and on too little evidence, pointing out that resistance to sulfonamide drugs alone is an inadequate diagnostic criterion. "In a large city hospital, such as the Philadelphia General, we observe a number of so-called sulfonamide-resistant pneumonias that later prove to be cases of tuberculosis, carcinoma, leukemia, etc." [16b]

In group C of table 2 are listed 7 cases of suppurative bronchopneumonia, of which 5 terminated fatally. This type of pulmonary inflammation has been carefully described by Neuhof,[17] and by Neuhof and Thomas.[18] The latter reported 120 cases, in 13 of which the patients were 60 years old and over. The death rate for the whole series was 24.2 per cent (29 deaths). In our experience the diagnosis in the aged may be overlooked clinically and only revealed at necropsy. The pathologic features of disease such as the frequency of purulent foci account for the lack of response to sulfonamide drugs. Neuhof and Thomas described the disease as "a severe bronchopneumonia involving one, several or many portions of the lung or lungs. Substantial portions of bronchopulmonary segments are involved. Spread from primary areas appears to be chiefly by the mechanism of spillover. Varying degrees of suppuration and necrosis occur within the affected segments of the lung, usually with the formation of single or multiple foci of liquefaction within areas of bronchopneumonia. Necrosis is at times outstanding and spectacular." They emphasized the role of these lesions in the lungs in the pathogenesis of empyema, pyopneumothorax and pulmonary abscess. The recovery in 2 cases in our series was aided by bronchoscopic drainage.

In group D of table 2 are listed the cases of pneumonia of undetermined origin, numbering 73 in all, with a mortality rate of 24.6 per cent. This category is unusually large because of the age of the patients. Collection and bacteriologic examination of specimens of sputum are interfered with by the lack of cooperation of the patient, by the death of the patient before an unsatisfactory specimen can be replaced with

16. (*a*) Plummer, N., and Ensworth, H. K.: Primary Atypical Pneumonia in General Hospitals and in Private Practice, Bull. New York Acad. Med. **20**:292-308 (May) 1944. (*b*) Flippin, H. I.: The Treatment of Primary Atypical Pneumonia, New York Med. **1**:11-14 and 20 (March 20) 1945.

17. Neuhof, H.: Suppurative and Necrosuppurative Bronchopneumonia: Their Surgical Aspects, Dis. of Chest **6**:299-305 (Oct.) 1940.

18. Neuhof, H., and Thomas, A.: Acute Suppurative Bronchopneumonia, Arch. Int. Med. **75**:45-64 (Jan.) 1945.

another, and by misplaced clinical emphasis, since in many cases the pneumonia is first detected on the autopsy table. Many of the cases listed here were probably due to pneumococci, since the response to sulfonamide therapy was prompt. It is also likely that a certain number of cases of virus pneumonia are included here. In the fatal cases in this group other serious diseases were regularly found in combination with the pneumonia.

CONDITIONS ASSOCIATED WITH PNEUMONIA

Among the conditions most frequently associated with pneumonia in the aged are cardiovascular, pulmonary, nutritional and cerebral diseases. In the cases in which the patients recovered, of which there were 131, we shall mention only the principal associated conditions. There were 48 patients with arteriosclerotic cardiovascular disease, including 2 with bundle branch block. Eleven patients were admitted with frank congestive heart failure. There were 10 cases of bronchial asthma, 8 of bronchiectasis, 11 with sufficient emphysema to be of clinical significance, 3 cases with cerebral complications and 11 cases of diabetes mellitus. These conditions existed either alone or, more commonly, in multiple combinations with the pneumonia. On the other hand, in the 33 fatal cases, arteriosclerotic heart disease was noted in 20. In 11 of these the patients were admitted with congestive heart failure. There were 3 cases of cor pulmonale and 2 cases of cerebral hemorrhage. There was emphysema of pronounced degree in 9 cases. Included in the fatal group were 6 cases of diabetes and 1 each of exophthalmic goiter, chronic enterocolitis, rheumatic heart disease, bronchial asthma, pulmonary embolism and cirrhosis of the liver.

In correlating the incidence of these associated conditions with the results obtained, it is immediately apparent that preexisting pulmonary disease is attended with far lower mortality than associated cardiovascular disease or diabetes. Pneumonia may be the factor which initiates heart failure or, occurring during the course of congestive failure, either aggravates the failure or interferes with the response to therapy. Peripheral vascular failure is far commoner than congestive heart failure in young persons and occurs late in the disease. Old persons are often admitted to the hospital with frank congestive failure complicated by an acute pneumonic process. Any infection may diminish tolerance to sugar and precipitate acidosis in diabetes. Likewise elderly persons with diabetes almost invariably show advanced arteriosclerosis affecting many parts of the body. The increased susceptibility of these patients to infections is well known but poorly understood.

The therapeutic results in the presence of complications demonstrate that the associated conditions may be treated successfully along with the pneumonia. In some of the complicated cases with fatal outcome

included in this series, the original illness furnished the substratum for the pulmonary infection, and the patients were admitted in moribund condition. Active treatment of the pulmonary infection and the associated conditions must be undertaken no matter how overwhelming the odds seem to be against recovery.

In addition to the influence of coexisting diseases, the diagnosis of pneumonia in an old person may be obscured by unusual modes of onset and by an atypical clinical course. In the aged these are more frequent and of different types than in younger age groups. The old often have a childlike attitude to disease and do not seek medical aid until the disease process is far advanced. Cases in which symptoms are referred to the abdomen often simulate surgical conditions. In this series there were 5 of this type, admitted at first to the surgical service with signs suggesting inflammation of the gallbladder or intestinal obstruction. Less well known is the so-called "apoplectiform" type of onset stressed by some of the older authors.[19] Here the clinical picture resembles that of a cerebral accident. This may range from evidences of cortical irritation, unilateral weakness, mental confusion, stupor and unconsciousness to actual hemiplegia. These neurologic signs are due either to toxemia or to temporary cerebral circulatory disturbance, since at autopsy no organic cerebral lesion can be shown. There was 1 such case in this series, with deep coma and one-sided twitchings at the beginning of the illness, in which the brain at necropsy was normal.

Complete latency of a pneumonic infection in the aged was first described in 1835 by Hourmann and Dechambre[20] in the dramatic account of the residents of the Salpêtrière, which was popularized in Charcot's famous lectures, "Old women do not even complain of malaise; no one in their dormitories—either among the attendants, housemaids, or neighbors—notices any change in their condition. They get up, make their beds, walk about, eat as usual, and afterward, feeling a little tired, they totter to their beds and expire. . . . The cadaver is opened, and a large part of the pulmonary parenchyma is found suppurating."[21] Aschoff has described a visit to an aged colleague who was apparently in good health. When notified of his demise only two days later, he expected to find evidence of so-called natural death, but postmortem examination revealed a malignant tumor of the thyroid

19. Schlesinger, H.: Die Krankheiten des höheren Lebensalters, Vienna, A. Hölder, 1914, vol. 1, pp. 334-335.

20. Hourmann, M., and Dechambre, R.: Recherches cliniques pour servir à l'histoire des maladies des vieillards, Arch. gén. de méd. **8**:405-428, 1835; **9**:338-357, 1836; **10**:268-296, 1836; **12**:27 and 165, 1836.

21. Charcot, J. M.: Leçons sur les maladies des vieillards et les maladies chroniques, Paris, A. Delahaye, 1868; translated by L. Hunt, New York, William Wood & Company, 1881, p. 27.

gland and lobar pneumonia in the stage of gray hepatization.[22] A recent study of sudden and unexpected natural death by Helpern and Rabson [23] showed that of 2,030 cases, death was due to disease of the respiratory tract in 23.2 per cent, and that in about one sixth of these fatal cases the patients were 60 years old or older. In their whole series lobar pneumonia was second to disease of the coronary artery in frequency, causing 8.7 per cent of the total of all sudden deaths in which autopsy was done. Next in frequency were bronchitis and bronchopneumonia (6.5 per cent), pulmonary tuberculosis (3.4 per cent) and pulmonary embolism and infarction (1.6 per cent).

Uncommonly the pneumonia may have a completely afebrile course. We encountered 2 such cases. A woman of 74 years whose temperature in five days of hospitalization never was more than 99 F., was given chemotherapy because of roentgenologic evidence of pneumonia. Postmortem examination confirmed the roentgenologic observation. The other was a man of 65 years with a long-standing emphysema and cor pulmonale whose temperature during eight days in the hospital rose only once to 100.8 F. and was normal during the remainder of the time. This patient did not receive chemotherapy. At necropsy extensive bronchopneumonia was present in both lower lobes; it was believed to be the cause of death.

Due to the fact that cerebral function in the aged is so frequently impaired by arteriosclerosis and parenchymal changes, toxic mental symptoms not infrequently dominate the course of illness to such a degree as to render management difficult. There were 4 patients in this series, only 1 of whom recovered, a man of 75 years with a blood culture positive for type I pneumococcus. Another became so uncontrollable that he climbed out of bed, fell and struck his head; he died four hours later in deep coma. The effect of toxemia on a brain with parenchymal degeneration and impaired circulation resulting from sclerotic vessels may also account for the mild confusional state which may occur after pneumonia in the old, and persist for varying periods of time, ranging from a few days to months.

In the aged the relapsing and recurrent forms of pneumonia are encountered in which the illness may spread over the course of several months. Such cases have been observed in the Home, pneumonia in one area responding to chemotherapy, with new involvement occurring later on cessation of treatment. Five or six such acute episodes over

22. Aschoff, L.: Zur normalen und pathologischen Anatomie des Greisenalters, Berlin, Urban & Schwarzenberg, 1938.

23. Helpern, M., and Rabson, S. M.: Sudden and Unexpected Natural Death: General Considerations and Statistics, New York State J. Med. **45**:1197-1201 (June 1) 1945.

the course of a few months are not unusual. Finally, at necropsy areas of old organized and recent pneumonia are found, often adjacent areas.

DIFFERENTIAL DIAGNOSIS

To establish the diagnosis of pneumonia in the aged, a careful history and physical examination are essential, but the symptoms, as we have indicated, may be masked, confusing or difficult to elicit. The signs are often entirely unreliable or uninterpretable, even when an extensive involvement is present, having been altered or hidden by the associated diseases or by lack of cooperation on the part of the patient. Sputum and blood cultures can give confirmatory evidence, although their value for specific therapy has become less. Because of the obstacles to accurate physical diagnosis our most valuable aid is the x-ray. That this method is not more widely used is either because facilities are not readily available or because the patient's condition is considered too critical for removal to the x-ray laboratory. More extensive utilization of mobile x-ray units which may be brought to the bedside will lead to greater diagnostic accuracy in the aged. But it is also true that even the roentgenogram may be misleading. Occasionally it may be found that, at the onset, the roentgenogram may be negative, even when physical signs are definitely present. Another exposure, after a short interval, will then show pneumonic infiltration. The following case report and the accompanying roentgenograms show how difficult it may be to differentiate pneumonia and pulmonary infarction.

Pulmonary Infarction.—A man of 85 years was admitted to the infirmary of the Home with pronounced cyanosis, dyspnea at rest, edema of the legs and a temperature of 102 F. There were signs of congestion at the base of the left lung and in the axilla. He was considered to have congestive heart failure and was treated accordingly. A roentgenogram showed what appeared to be a typical infiltration in the lower part of the upper lobe of the right lung and also at the base of the lower lobe of the right lung adjacent to the right cardiac border. As his temperature had become normal and his general condition improved, no chemotherapy was given. A week later a second roentgenogram showed a gradual resolution of the infiltration in the right lung with the appearance of an area of recent infiltration in the upper portion of the lower lobe of the left lung. Eight days later another roentgenologic examination showed the areas in the upper lobe of the right lung to be cleared, with the infiltration in the left side also clearing. Some infiltration persisted in the lower lobe of the right lung. The clinical impression was of a silent bronchopneumonia complicating congestive heart failure. Four days later he died suddenly. At necropsy an organized infarct was found corresponding to the shadow in the upper lobe of the right lung, a broken-down infarct in the apex of the lower lobe of the left lung and an area of atelectasis in the lower lobe of the right lung (figs. 1, 2 and 3).

This case illustrates but one of the conditions involved in the differential diagnosis of pneumonia in the aged. Space limitations permit only the mention of diseases which may simulate pneumonia, such as

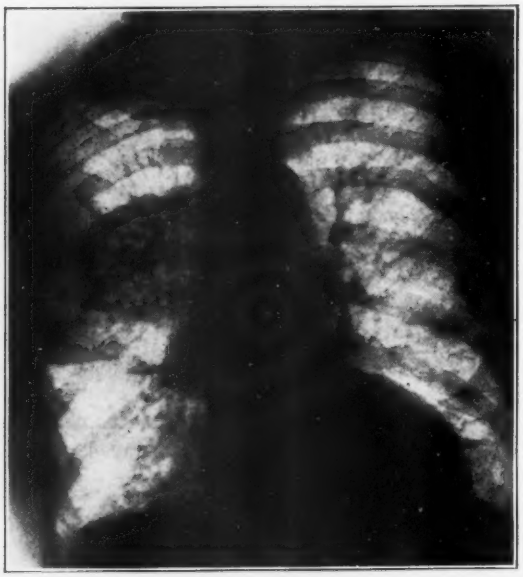

Fig. 1.—Roentgenogram of the chest of an 85 year old man under treatment for congestive heart failure, showing infiltration in the lower part of the upper lobe of the right lung, interpreted as pneumonic in character.

Fig. 2.—Roentgenogram of the chest of the same person, one week later, showing the disappearance of infiltration in the upper lobe of the right lung and the appearance of lesion in upper part of the lower lobe of the left lung.

(1) coronary thrombosis with myocardial infarct and early pulmonary edema, (2) congestive heart failure with or without pulmonary infarct, (3) pulmonary embolism arising often from a silent phlebothrombosis of the lower extremities,[24] (4) pulmonary abscess, (5) bronchostenosis either from foreign bodies or from neoplasms, (6) pulmonary atelectasis of either the lobar (massive collapse) or lobular type, (7) pulmonary neoplasms, both primary and metastatic, (8) metastatic septic foci, (9) pulmonary tuberculosis, (10) bronchiectasis and (11) the chronic lipid pneumonias. Before diagnosing pneumonia in the aged all of the foregoing must be seriously considered and ruled out. The facile diagnosis of pneumonia based on the presence of cough, fever and a few

Fig. 3.—Roentgenogram of the chest of the same patient, eight days later, showing the disappearance of lesions in both the right and the left lung.

moist rales at the bases of the lungs is to be avoided, and every effort must be made to establish a diagnosis based both on the pathologic anatomy and on the bacteriologic examination.

The principal complications other than those connected with the associated diseases are empyema, meningitis and endocarditis. All

24. White, P. D.: Pulmonary Embolism and Heart Disease: Review of Twenty Years of Personal Experience, Am. J. M. Sc. **200**:577-581 (Nov.) 1940. Homans, J.: Pulmonary Embolism Due to Quiet Venous Thromboses and Simulating Cardiac and Pulmonary Disease, New England J. Med. **229**:309-314 (Aug. 19) 1943. Ask-Upmark, E.: Occurrence of Thrombosis and Pulmonary Embolism in Pneumonia, Acta med. Scandinav. **113**:286-303 (March 18) 1943.

recent reports [25] have noted the lower incidence of empyema in all age groups since the advent of chemotherapy. Two cases of empyema were encountered, one of which, in an 84 year old man, is worthy of comment because of the excellent effect of penicillin, administered intrapleurally and intramuscularly.

Empyema.—Patient A. J., an 84 year old man, had noted cough, fever and pain in the chest two weeks previously, which had apparently yielded to sulfonamide medication. When first seen he was cyanotic and dyspneic, with his temperature elevated to 101 F. The peripheral vessels were sclerotic; the pulse was totally irregular, and his heart was enlarged. Because of dulness and distant breath sounds at the base of the right lung, exploratory aspiration of the chest was performed, which yielded thick blood-tinged pus. On culture Pneumococcus type III was isolated, which was found to be one quarter as resistant to penicillin as the standard organism. Intramuscular penicillin therapy, 15,000 units every four hours, was begun. Potain aspiration of the right pleural cavity yielded 200 cc. of purulent fluid, and 30,000 units of penicillin was injected intrapleurally. These procedures were continued daily for one week until a total of 800,000 units intramuscularly and 230,000 units intrapleurally was administered. The gradual clearing of the shadow is of particular interest, since treatment was given for only one week, at which time the purulent fluid obtained from the pleural cavity had become sterile. The patient was observed in the hospital for two weeks after cessation of active therapy. Since he felt well, was entirely afebrile and suffered no discomfort from the residual effusion, he was discharged to his home. Figure 4 *A* shows the effusion at the time of diagnosis, figure 4 *B*, *C* and *D* at one month, two month and five month intervals. Particular attention is directed to the very gradual resolution of the intrapleural shadow over a period of months.

This result in a man of advanced age is in accordance with the experience of Rudensky, Sprong and Woods [26], Hirshfeld, Buggs, Abbott and Pilling [27] and Healy and Katz,[28] all of whom treated much younger patients. Of decisive importance in our case was the small size of the pleural effusion. Had it been larger, surgical intervention might have been obligatory in order to relieve respiratory embarrassment, even

25. Hurwitz, S., and Stephens, H. B.: Empyema in Children, J. Pediat. **14**: 11-20 (Jan.) 1939. Schwartz, L.; Flippin, H. F., and Turnbull, W. G.: Treatment of Pneumococcic Pneumonia: A Comparative Study of Three Hundred and Fifty-One Patients Treated at the Philadelphia General Hospital, Ann. Int. Med. **13**:1005-1012 (Dec.) 1939. Flippin, H. F.; Schwartz, L., and Rose, S. B.: Comparative Effectiveness and Toxicity of Sulphathiazole and Sulphapyridine in Pneumococcic Pneumonia, ibid. **13**:2038-2049 (May) 1940.

26. Rudensky, H.; Sprong, D. H., Jr., and Woods, C. C.: The Medical Treatment of Acute Empyema, J. A. M. A. **128**:573-577 (June 23) 1945.

27. Hirshfeld, J. W.; Buggs, C. W.; Abbott, W. E., and Pilling, M. A.: The Value of Penicillin in the Treatment of Empyema, J. A. M. A. **128**:577-582 (June 23) 1945.

28. Healy, M. J., Jr., and Katz, H. L.: The Treatment of Empyema Thoracis with Penicillin, J. A. M. A. **128**:568-573 (June 23) 1945.

though the fluid was sterile. The absence of loculation was also a favorable feature. The gradual disappearance of the effusion over a period of months and the excellent reexpansion of the lung are particularly noteworthy.

Until the introduction of the sulfonamide drugs pneumococcic meningitis was almost invariably fatal. The optimal treatment today, as reported by Sweet, Dumoff-Stanley, Dowling and Lepper,[29] consists of intramuscular and intrathecal injections of penicillin combined with

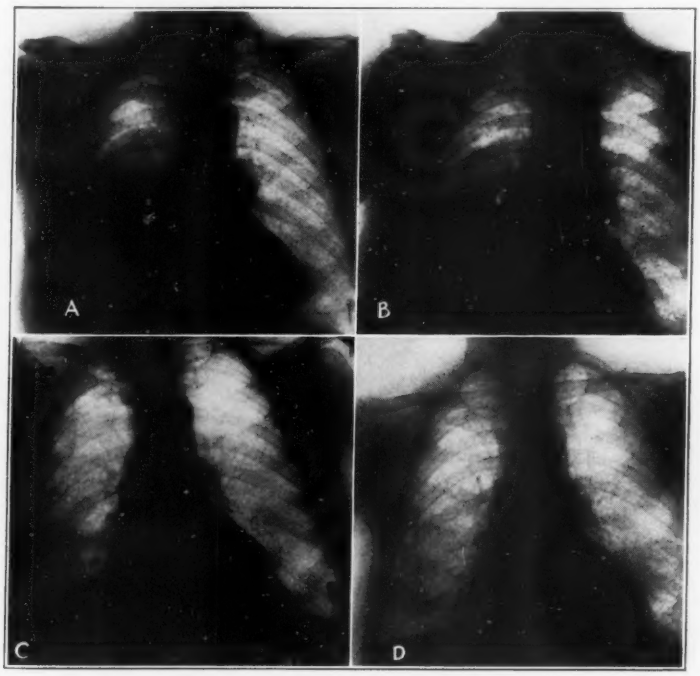

Fig. 4.—*A*, roentgenogram of the chest of an 84 year old man showing effusion in the right pleura. *B*, roentgenogram of the chest of the same patient, one month later, after completion of penicillin therapy, showing only slight diminution in size of effusion and small amount of air in right pleural cavity. *C*, roentgenogram of the chest of the same patient, two months later, showing pronounced diminution in size of effusion. *D*, roentgenogram of the chest of the same patient, three months later, showing only residual thickening of the right pleura.

the administration of sulfonamide drugs. In their series of 16 cases of pneumococcic meningitis treated with penicillin with and without

29. Sweet, L. K.; Dumoff-Stanley, E.; Dowling, H. F., and Lepper, M. H.: The Treatment of Pneumococcic Meningitis with Penicillin, J. A. M. A. **127**:263-267 (Feb. 3) 1945.

sulfonamide drugs, there were 7 recoveries. Thus, there was a mortality rate of 56 per cent as compared with a rate of 93 per cent in 40 cases of the disease treated only with sulfonamide drugs. Included in our series of pneumonia cases is that of a man aged 74 years suffering from a Pneumococcus type II infection of the meninges as well as of the lungs and blood stream, in which an excellent result was obtained by combined therapy.

Pneumococcic Meningitis.—A man aged 74 had noted fever up to 102 F. and pain in the left side of the chest four days before admission. Three days previously the temperature rose to 103.6 F., and signs at the base of the left lung were detected by his physician, who made a diagnosis of bronchopneumonia and administered penicillin, totaling 400,000 units. His temperature fell to 100.2 F., but on the day of admission the patient became restless, disoriented and confused. He was found to be acutely ill, moaning and unresponsive. His neck was rigid and the Kernig reflex was present bilaterally. A few sticky rales were heard at the base of the left lung. Lumbar puncture yielded a cloudy fluid containing 1,300 cells of which 50 per cent were polymorphonuclear cells. Pneumococci were found on direct smear, which when cultured proved to be type II. The same organisms were recovered from the blood stream. The electrocardiogram showed evidence of hypertrophy of the left ventricle and myocardial damage. Blood pressure was 110 systolic and 80 diastolic. Hemoglobin was 76 per cent; white blood cells numbered 27,000, with 93 per cent polymorphonuclear cells.

He was given an initial dose of 2 Gm. of sulfadiazine intravenously, and 1 Gm. every four hours. Penicillin was given intramuscularly in an intial dose of 100,000 units and in subsequent doses of 25,000 units every three hours. On the morning after admission penicillin was given intrathecally, 100,000 units being injected due to an error, as only 10,000 units had been ordered. In spite of therapy the patient's condition remained unchanged, rigidity of the neck and coma persisting. Fluids and medication were administered through a small caliber (Levin) gastric tube. Thirteen hours after the dose of 100,000 units of penicillin intrathecally, the spinal fluid level was 570 units per cubic centimeter. The spinal fluid culture became negative and remained so for the rest of the hospital stay. Leukocytosis and low grade fever continued. The spinal fluid cell count rose to 13,000 the day after the injection of penicillin and dropped to 2,000 the next day. Three days after the first dose, 10,000 units of penicillin was injected intraspinally, at which time the fluid cells were 180. On the sixth hospital day the cell count was 580. On the seventh hospital day 10,000 units of penicillin was again given intrathecally. Coma and confusion persisted until the tenth day following admission, when the patient began to make steady progress with clearing of the sensorium and diminution of the rigidity of the neck. In a few days the patient had completely regained his faculties. Three weeks following admission the spinal fluid was clear with a cell count of 33. Administration of penicillin intramuscularly and of sulfadiazine by mouth was stopped three weeks after the beginning of therapy. At the time of his discharge, one month after his admission, the patient was asymptomatic and afebrile, although the white blood cell count was still elevated to 13,000 with a normal differential count, and the last lumbar puncture one week before discharge still disclosed 16 cells.

Pneumococcic Endocarditis.—While no cases of pneumococcic endocarditis occurred in this series, one of us (F. D. Z.) has

reported elsewhere 9 cases of acute bacterial endocarditis in the aged of which 3 were due to pneumococci, and 1 was due to a mixed infection by type XI pneumococci and hemolytic streptococci.[30] Thayer[31] and Ruegsegger[32] have directed attention to the occurrence of pneumococcic infections of the heart valves in the higher age groups. Tinsley in a recent review of the subject states, "Pneumococcic endocarditis occurs in about 3 to 3.5 per cent of all pneumococcic infections and is responsible for probably about 5 to 10 per cent of deaths due to pneumococcic infections." In his 16 cases the ages ranged from 27 to 84 years, the average being 50 years. Eleven of the patients were above 45 years of age.[33]

PROGNOSIS AND TREATMENT

Many of the factors governing the prognosis in pneumonia in the aged have already been mentioned, such as the multiplicity and severity of the associated diseases, and the high mortality has been pointed out in cases with apoplectiform onset and with the toxic psychoses, as well as in those in which the disease has an afebrile course or in which cardiac complications develop. In all except 4 of our fatal cases there was multiple lobe involvement. Pneumococcus III infection has always been considered as accompanied with an unusually high mortality rate, especially in the aged. In 65 cases due to pneumococci, there were 16 cases (25 per cent of the total) of type III pneumococcus infection of which only 3 were fatal, but these represented 37.5 per cent of the total deaths in the pneumococcus series. Type III infections, although responding well to modern chemotherapy even in the aged, are nevertheless formidable invaders. Pneumococcus type XX likewise seems to possess high virulence.

The prompt recognition of the existence of a pneumonia and the early use of chemotherapy with appropriate supportive measures constitute the essential factors in treatment of pneumonia in the aged. The drastic lowering of the mortality rate of the group here presented is ample proof of the value of sulfonamide drugs in treatment of pneumonia in the old. That the aged can tolerate them is also well demonstrated. The small series treated with penicillin, 11 cases with no mortality, leads to high hopes for the future, particularly in the cases with preexisting heart disease. In cases without evidence of cardiac damage we make

30. Zeman, F. D., and Siegal, S.: Acute Bacterial Endocarditis in the Aged, Am. Heart J. **29**:597-610 (May) 1945.

31. Thayer, W. S.: Studies on Bacterial (Infective) Endocarditis, Johns Hopkins Hosp. Rep. **22**:1-185, 1926.

32. Ruegsegger, J. M.: Pneumococcic Endocarditis, Arch. Int. Med. **62**:388-400 (Sept.) 1938.

33. Tinsley, C. M.: Pneumococcic Endocarditis, Arch. Int. Med. **75**:82-88 (Feb.) 1945.

a practice of administering sulfonamide drugs first, switching to penicillin only when no benefit is observed after seventy-two hours, or if the patient cannot tolerate the drug.

In a recent paper on the treatment of pneumococcic pneumonia with penicillin Meads, Harris and Finland [34] have enumerated the general indications for penicillin, and their recommendations are particularly appropriate for aged patients.

> Penicillin is the treatment of choice and should be used from the start in the following cases: in patients who are extremely ill and in a shocklike state; in patients with severe cardiac, renal or hepatic damage, particularly if there is edema or azotemia; if there is severe leukopenia; and in patients who are known to be sensitive to sulfonamides and have rashes, fever or severe nausea and vomiting early in the course of treatment with these drugs.
>
> A change to penicillin from sulfonamides is indicated in patients who have received adequate doses and attained adequate blood levels but have failed to respond with improvement in the symptoms and a significant drop in temperature and pulse rate after twenty-four hours or longer, particularly if there is spread of the pulmonary lesion, persistent bacteremia or an increase in the number of pneumococci in the sputum as seen in direct smears; this change is also indicated if leukopenia, delirium tremens, auricular fibrillation or pulmonary edema develops before the symptoms of pneumonia have cleared or if severe untoward reactions, such as acute hemolytic anemia, gross hematuria, oliguria, anuria, nitrogen retention or even drug rash, occur before the pulmonary infection has been controlled. Crystalluria or microscopic hematuria need not be considered a cause for stopping sulfonamides but is an indication for alkalies and for increasing the fluid intake. Penicillin may be used locally when infected pleural fluid or other accessible foci of infection develop, and oral sulfonamides may be continued in such cases.

In the active treatment the patient should be made comfortable in bed, and encouraged to change his position and to move his legs. The question of the proper use of rest in bed is a subject which has again become a matter of active discussion.[35] It is interesting to note how medical opinion has changed with the passage of time. Formerly it was considered unwise to keep old persons in bed because it was believed that this encouraged the development of pulmonary congestion and pneumonia. Today most of the objections to prolonged rest in bed are based on the increased tendency to the formation of peripheral venous thrombi with subsequent pulmonary embolism. We do not feel that rest in bed itself leads to pneumonia in the aged unless the patient is immobilized by a plaster cast or constricting bandages or is unconscious. Phlebitis with the formation of thrombi may be avoided by leg exercises

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34. Meads, M.; Harris, H. W., and Finland, M.: Treatment of Pneumococcal Pneumonia with Penicillin, New England J. Med. **232**:747-755 (June 28) 1945.

35. Levine, S. A.: Some Harmful Effects of Recumbency in the Treatment of Heart Disease, J. A. M. A. **126**:80-84 (Sept. 9) 1944; Use and Abuse of Bed Rest, Conferences on Therapy, New York State J. Med. **44**:724-730 (April 1) 1944.

and frequent changes in position. We have no fear of keeping old persons in bed until they are well if these precautions are taken. Having established the patient with pneumonia in bed, we see that he is kept as comfortable as possible with attentive nursing care and with the judicious use of sedatives. Codeine and related drugs to control the cough must be given sparingly, since excessive depression of the cough reflex may lead to accumulation of viscid sputum in the smaller bronchi and the development of areas of atelectasis.[36]

The fluid intake is guided in part by the state of the cardiovascular system, but when sulfonamide drugs are given the urinary output should be kept at 1,500 cc. daily. The diet is maintained as far as possible in accordance with the desires of the patient, but the patient's nutritional status must be evaluated on the basis of history, physical findings and blood studies. Vitamin deficiencies and hypoproteinemia should be sought for and treated actively. Sulfonamide therapy should be started promptly with an initial dose of 4 Gm. given as one dose or fractionally over the course of a few hours, and then maintained at 1 Gm. every four hours throughout the day and night. Each dose of the sulfonamide drugs were used in this manner. The earlier patients bicarbonate. In the series of cases under consideration, all forms of the sulfonamide drugs were used in this manner. The earlier patients in the series were given sulfapyridine and the later ones sulfathiazole or sulfadiazine with the occasional use of sulfamerazine. Sulfadiazine and sulfathiazole were better tolerated than the sulfapyridine and there were few cases in which they had to be stopped because of gastrointestinal symptoms.

Throughout the entire course the blood count and urine must be frequently checked, at least every other day. Blood level determinations are useful in cases in which nonabsorption of the drug is suspected. In only 1 case was it necessary to stop because of renal involvement, and in 1 case because of leukopenia. Dosages in the favorable cases are to be maintained for at least three to four days after the subsidence of temperature and then in smaller doses for the remainder of a week. In none of our fatal cases can it be said that the use of the sulfonamide compounds contributed toward an untoward result. Specific serum was used in 4 cases, in each instance as an adjuvant to chemotherapy. The indication for the use of serum was an extreme toxemia, a positive blood culture or a drug idiosyncrasy, although other severely toxic patients both with and without bacteremia responded to sulfonamide drugs alone. Today there seems to be far less need for serum therapy. Penicillin was

36. Finland, M., and Loverud, H. I. L.: Massive Atelectatic Collapse of the Lung Complicating Pneumococcus Pneumonia, Ann. Int. Med. **10**:1828-1847 (June) 1937.

administered intramuscularly in doses of 15,000 to 20,000 units every three hours.

The importance of combining specific therapy with carefully planned supportive therapy has been stressed by Armstrong, England, Favour and Scheinberg,[37] who point out that one may expect to see new clinical pictures in connection with pneumonia, as specific and bacterial agents permit prolonged survival in the face of infections otherwise rapidly fatal. One of their 2 examples is an 85 year old man who had previously been undernourished and who had pneumonia following a suprapubic prostatectomy. The pulmonary infection was slowly brought under control with sulfonamide drugs and penicillin. This drug also served by intrapleural injection to clear up an effusion in the right pleura. The real problem had to do with the patient's impaired nutrition as indicated by the reduction of the plasma proteins to 3.3 Gm. per hundred cubic centimeters. This was further aggravated by nausea, vomiting and diarrhea. In addition a severe anemia was found, the red cells at the low point being 2,900,000 per cubic millimeter and the hemoglobin 8.2 Gm. per hundred cubic centimeters. To combat the hypoproteinemia and the anemia whole blood was given in six transfusions to the total of 2,900 cc.; plasma was given fifteen times, totaling 4,550 cc., and amino acids were administered by mouth to the amount of 3,330 cc. As a result of this truly heroic treatment the patient recovered.

The use of oxygen inhalation is a valuable adjuvant, especially when pulmonary absorption has been impaired by associated cardiovascular or respiratory disease. The administration by oxygen mask seems to be the preferable method, as it is well tolerated by the aged person and does not interfere with nursing care. Recent studies emphasize the need for starting oxygen therapy before the anoxia becomes obvious.

The treatment of the associated diseases is equal in importance to the specific therapy of the pneumonia. Diabetes must be controlled with insulin and dietary measures. Digitalis, although not a routine measure, must be employed in those cases in which there is auricular fibrillation or obvious congestive heart failure, or which present early signs of cardiac insufficiency. Mercurial diuretics may be employed to advantage when frank congestive failure is present. By combining active treatment of the failing heart with use of the antibacterial drugs one may expect even greater reduction in mortality.

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37. Armstrong, S. H., Jr.; England, A. C.; Favour, C. B., and Scheinberg, I. H.: Anemia and Hypoproteinemia Complicating Severe Protracted Pneumonia, J. A. M. A. **127**:303-306 (Feb. 10) 1945.

CLASSIFICATION OF PULMONARY INFECTIONS

Since the series of cases which has been presented is relatively small and fails to give the whole picture of pulmonary infections seen in the higher age groups, the complete classification presented in table 4 will aid in analyzing the varieties of pneumonia occurring in the aged. A few brief explanatory comments will suffice on the types of pneumonia occurring in the aged which have not already been discussed. Mycobacterium tuberculosis as a cause of pneumonia in the aged must never be forgotten, and the organisms must be searched for in the sputums of all patients with persistent signs referable to the lungs, or whose illness resists specific therapy. Roentgenologic examination may be misleading. Pasteurella tularensis as the causative agent in the pneumonia of old age is mentioned here for the sake of completeness.[38] Ornithosis, the recently recommended designation for psittacosis and related conditions,

TABLE 4.—*Classification*

A. Pneumonia due to specific organisms
   1. Diplococcus pneumoniae
   2. Streptococcus pyogenes
   3. Staphylococcus aureus
   4. Klebsiella pneumoniae
   5. Mycobacterium tuberculosis
   6. Pasteurella tularensis
B. Pneumonia due to filtrable viruses
   1. Ornithosis
   2. Primary atypical pneumonia ("virus pneumonia")
   3. The pneumonia of epidemic influenza
C. Suppurative bronchopneumonia (Neuhof)
D. Pneumonia of undetermined bacteriologic origin
E. Aspiration pneumonia
   1. Chronic lipid pneumonia
   2. Pneumonia following aspiration of stomach contents
   3. Foreign bodies in the bronchi
F. Postoperative pneumonia
   1. Associated with antecedent infection of the upper respiratory tract
   2. Associated with chronic cardiovascular or pulmonary disease
   3. Associated with lobar or lobular atelectasis due to:
      a. too profound anesthesia
      b. too much sedative medication
      c. shock and hemorrhage
      d. constricting bandages or plaster casts

is caused by a virus transmitted by parrots, canaries, pigeons, chickens and other birds. There are many similarities between this type of pulmonary inflammation and that which is now termed "primary atypical or virus pneumonia." One opinion, as expressed by Favour,[39] is that the virus is the same and has become fixed in man and incapable of heterogeneous parasitism. The experience of the Commission on Acute Respiratory Diseases of the United States Army is directly opposed to this view. Dingle [40] states that the great majority of cases of primary

38. Stuart, B. M., and Pullen, K. L.: Tularemic Pneumonia: Review of American Literature and Report of Fifteen Additional Cases, Am. J. M. Sc. **210**: 223-236 (Aug.) 1945.

39. Favour, C. B.: Ornithosis (Psittacosis), Am. J. M. Sc. **205**:162-187 (Feb.) 1943.

40. Dingle, J., and others: The Present Status of the Etiology of Primary Atypical Pneumonia, Bull. New York Acad. Med. **21**:235-262 (May) 1945.

atypical pneumonia observed in army hospitals is not caused by psittacosis or related viruses. In the commission's three years of experience the diagnosis of psittacosis or ornithosis has not once been established in a series of more than 500 cases of atypical pneumonia and related respiratory infections.

The chronic lipid pneumonias are thought to be more prevalent than is generally realized, especially in the aged. The administration of medication in oily sprays and nasal drops is responsible for large collections of oil with surrounding fibrosis in the bronchopulmonary tree, which may later become infected.[41] The aspiration of stomach contents into the trachea and bronchi with a subsequent pneumonia may occur postoperatively, either while the patient is still under the influence of the anesthesia or as the result of regurgitation from a dilated stomach or during unconsciousness from any cause such as a cerebral injury, a cerebral accident or attempts at suicide with hypnotic drugs.[42] The postoperative pneumonias are mentioned here because of the increasing number of operations performed on aged persons. The problems presented by these cases deserve special consideration, and for this reason no cases have been included in our present series, although some of the important features are enumerated in table 4.

These groups are not always clearcut and may actually overlap. The organism identified by methods of sputum culture may at times be only an incidental finding, whereas in cases classified as having the bacterial origin undetermined, it may be that either no attempt was made to identify an organism or that it was impossible to obtain material for identification. Too frequently this is true in cases involving the aged, in which the pneumonia may have been overlooked, or the patient may not have cooperated, or the patient may have died before additional specimens of sputum could be obtained.

SUMMARY

One hundred and sixty-six cases of pneumonia in men and women 60 years of age and older have been studied. Of these, 33 cases, or 20 per cent, were fatal. Included in the series are 65 cases due to various types of pneumococci, of which 8 terminated fatally, or 12 per cent. Sulfonamide therapy was used in 128 cases. Additional type-

41. Bishop, P. G. C.: Oil Aspiration Pneumonia and Pneumolipoidosis, Ann. Int. Med. **13**:1327-1359 (Feb.) 1940. Freiman, D. G.; Engelberg, H., and Merritt, W. H.: Oil Aspiration (Lipoid) Pneumonia in Adults, Arch. Int. Med. **66**:11-38 (July) 1940. Cannon, P. R.: The Problems of Lipid Pneumonia, J. A. M. A. **115**:2176-2179 (Dec. 21) 1940.

42. Irons, E. E., and Apfelbach, C. W.: Aspiration Bronchopneumonia, with Special Reference to Aspiration of Stomach Content, J. A. M. A. **115**:584-587 (Aug. 24) 1940.

specific serum was given in 5 of these cases. Penicillin was used successfully in 11 cases, including an empyema due to type III pneumococci in a man aged 84 years and a meningitis due to type II pneumococci in a man aged 74 years.

Although the mortality has been dramatically reduced by recent advances in therapy, pneumonia is still a disease with high incidence and high mortality in the aged. With the proper appreciation of the complex problems encountered in the old, and with better methods of treatment, one may look for further improvement in the results. The disease appears in unusual forms both in its onset and in its course in the aged, and is commonly associated with other conditions which may obscure and aggravate it. Physicians should be on the alert for pneumonia in the aged, recognize it when it is present and treat it actively in spite of what may appear to be overwhelming obstacles. Its occurrence should not be assumed merely because of its prevalence in the aged or because of the presence of a few rales at the bases of the lungs. The period of medical development is past when an unqualified diagnosis of pneumonia on the death certificate of an elderly person was considered adequate because no one expected old persons to recover from the disease.

Progress in Internal Medicine

ALLERGY

A Review of the Literature of 1944 and 1945, with Comments on Future Problems

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DURING the war there has been little opportunity for careful study of such a chronic disease as allergy. With a few exceptions the medical officers in the Army have been unable to accomplish much beyond the clinical classification of their patients, and in civilian life the pressure of routine work has precluded comprehensive or thoughtful studies. Now, however, the war is over, our young physicians are coming back slowly but surely and one can expect that before long opportunities for intensive full time work in the form of residencies and fellowships in allergy will become available and so make further progress possible. In a recent number of the *Atlantic Monthly,* Prof. Harlow Shapley [1] has written a striking paper. After describing the "advantages" of war—the full employment, the large wages, the increase in circulating currency and, above all, the unity of purpose and action—he pointed to what might happen if this same unity of purpose could be applied to the advancement of science. If cooperation could be fully established, even a small fraction of the effort and the expense of war applied to peace might result in extraordinary benefit to everybody. Professor Shapley suggested that if every scientific investigator would write down the questions which he needs to have answered in his own research it might easily happen that one of his fellows, even though working in a different field, might know the answer or at least give him a suggestion which would help him promptly and effectively. It is the unity of purpose which is so important.

The recent literature on allergy is not impressive either in volume or in content, but in reviewing it I shall try to point to some of the questions which trouble me.

In the allergy clinic, one sees a variety of symptoms. There are hay fever, asthma in young people and eczema in each of which the histories usually show a clear relation between the symptoms and the changes in environment or diet. The positive reactions to skin tests observed are anticipated, and they confirm the diagnosis. For these

1. Shapley, H.: A Design for Fighting, Atlantic Monthly **176**:107, 1945.

conditions allergy by itself appears to be an adequate explanation. But there are other cases, in which the diagnosis is not so easy. There is chronic rhinorrhea called vasomotor rhinitis, there is asthma beginning after a person has reached the age of 40, there are cutaneous lesions not readily explained and there is migraine headache. In addition, in the patient with severe asthma complications develop: Polypoid sinusitis is common. Periarteritis nodosa and Loeffler's syndrome are not so common. Peptic ulcer and gastric hemorrhage have been seen. Then, more recently, from the Pacific have come a few patients with "tropical eosinophilia."

All these patients are grouped together chiefly because their symptoms are so similar; they are also grouped together because any and all combinations of these symptoms occur either together or in sequence and finally because inheritance of the "asthmatic state" seems to establish the "allergic person" as one who is more likely than his fellows to have one or another of the symptoms listed develop. The term "asthmatic state" has in this sense a broader meaning than the term "allergy." It is the background on which allergy may develop. Also it is the background from which asthma from other causes beside allergy may come. It indicates a reaction pattern which is characteristic. Let it be called x.

A patient who has x and who has eczema in infancy will be more likely than others to have hay fever and asthma develop later. He is not nearly so likely to have arthritis or gastrointestinal disturbances develop. Why stop to consider an x for asthma and allergy when another philosopher might suggest a y for arthritis or a z for mucous colitis? Is the group of patients with "allergic" manifestations any more characteristic than the group with arthritis? I think so, chiefly because of the evidence that the asthmatic state is a disturbance which not only is generalized but runs true to its form. In passing, one can observe that for each person the reaction pattern appears to be uniform and fairly constant. Hay fever, asthma and eczema—each symptom tends to recur in the individual patient, and the fact suggests a local change in the tissue rather than a generalized change. However, when the primary process increases in severity and goes "out of control," then other manifestations in the same symptom group may be added to the picture. Severe hay fever leads into asthma and sometimes to urticaria as well. Combinations of eczema and asthma are found, and the combination of chronic vasomotor rhinitis and asthma with thick membrane in the sinuses is typical enough.

It is the multiplicity of typical symptoms occurring together or at different times in the same patient which forces the conception of a generalized disease entity. In the allergic patients the positive reactions to skin tests and the antibodies (reagins) in the blood serum confirm

the theory, and then, finally, when the person marries his children are more likely than others to have manifestations of allergy develop. The evidence of a "constitutional" change is ample. More studies of the natural history of the allergic patient will throw a sharper light on the process. Clein [2] has made a ten year study of 100 allergic children, but 100 children are not enough and ten years are not enough. The histories of many patients in whom asthma has developed in their thirties and forties show that they, too, had eczema in infancy. How often does this infantile eczema subside in two or three years to leave the child perfectly normal for the rest of his life, and, on the other hand, how often is this early symptom of allergy followed later by the development of other manifestations? Is there any characteristic of the early disease which would throw light on the ultimate prognosis? As Clein points out, eczema is the first symptom in early childhood, but rhinitis and hay fever are the important symptoms later on. Whereas the symptoms of allergy change from time to time, the fundamental allergic state continues, and so it is that these persons are the ones in whom asthma develops later in life; perhaps also they are the ones in whom reactions to the sulfonamide drugs or penicillin develop or who show such alarming symptoms as were described by Sprague and Barnard [3] in a soldier who reacted violently to yellow fever virus because he had retained his sensitiveness to egg. Presumably patients in whom asthma develops for the first time after they have reached the age of 40 also have *x*, and presumably patients with primary organic emphysema do not have *x*. It will take many statistical studies to make sure about these things. The point of this argument is that further knowledge of the asthmatic state should reveal the basic nature of the disease and so lead to a new approach to its treatment. So far the best one can do is to say that it is inherited.

The immediate cause of each symptom is a physical change in the local tissues. The lesions and the symptoms which they produce are listed in the table. One observes that these lesions are reversible and that one can ascribe each of them to a disturbance which is "vasomotor" in the broad sense. Each of the symptoms occurs in attacks.

The exciting cause of the local disturbance has been considered to be histamine or at least H substance, but then comes the question: Is the trouble due to excessive release of histamine, or is it due to excessive reaction to the normal quantity? What starts the process?

2. Clein, N. W.: The Growth and Development of Allergy: A Ten Year Study of One Hundred Allergic Children from Birth to Ten Years of Age, Ann. Allergy **1**:3, 1945.

3. Sprague, H. B., and Barnard, J. H.: Egg Allergy, U. S. Nav. M. Bull. **45**:71, 1945; abstracted, J. A. M. A. **129**:578 (Oct. 20) 1945.

Allergy can do it, but evidently there are other mechanisms as well. As will be described later, there is depletion in both the somatic and the psychic sense; there is infection, and there is intoxication by drugs. Each of these factors can cause asthma, but whether the action is in each case produced by the release of H substance remains to be demon-

Lesions of Allergy and the Symptoms Which They Produce

Lesions	Symptoms
Vasodilatation	Eczema, erythema (migraine ?)
Vasoconstriction	Eczema (migraine ?)
Smooth muscle spasm	Asthma, colic
Increased activity of the glands	Asthma, hay fever, hydrorrhea due to vasomotor neurosis
Increased permeability of the capillaries	Hay fever, urticaria
Narrowing of the blood vessels	Periarteritis nodosa, purpura
Hemorrhages of the mucous membrane	Peptic ulcer
Hypoplasia of the bone marrow	Agranulocytosis, purpura, anemia
Shifts in blood cell counts	Eosinophilia
Lesions of the joints (?)	Arthritis ?

strated. The relationship between these factors can be summarized in a diagram (see the chart).

In general one can postulate for the development of "allergic symptoms" the following requirements: (*a*) a person with a certain inheritance (asthmatic state) has (*b*) the capacity to develop sensitiveness

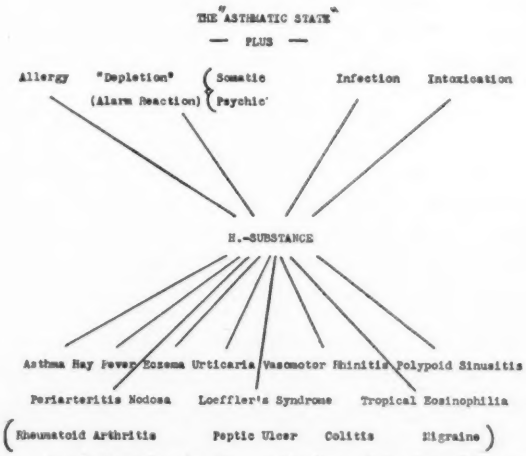

Diagram of relationships in the production of "asthmatic" symptoms.

(allergy) and also (*c*) the capacity to produce and/or to react to H substance so as to cause (*d*) a variety of symptoms of vasomotor origin.

Each of these topics can now be considered in some detail, but, first of all, how common is the asthmatic state?

The incidence of the asthmatic state is hard to define in precise figures. Hyde and Kingsley [4] rejected for allergy only 495 out of 60,000 draft registrants—less than 1 per cent. One can hope that later on the medical history of the war will produce still other figures like this. Among the diseases of the total patients admitted to any military hospital, allergy ranks high. In several areas asthma ranks third among the disabling diseases. Psychic and gastrointestinal disorders come first and second respectively. At the Percy Jones General Hospital, Alford [5] found that asthmatic patients constituted 10 per cent of all persons admitted. Colonel French,[6] who has been so enthusiastic and persistent with the organization of allergy clinics in the Fourth Service Command, reported 9,591 patients with asthma, 5,373 with hay fever, 3,831 with perennial allergic rhinitis and over 4,000 with miscellaneous diseases from a total number of 32,000 patients examined in the fifty clinics under his direction. As outlined in a previous review,[7] patients who received discharges from military service because of asthma vary from 3 to 6 per cent of those admitted to the hospital. It is obvious that the problem of allergy is large.

The asthmatic state—the *x*—concerns allergy in particular, but, as the diagram shows, the same symptoms may arise from other exciting causes. Depletion is one, and it has two parts: somatic and psychic. There are patients in whom poor health in general, with loss of weight and strength, appears to be sufficient cause for the asthma or the chronic rhinitis or the urticaria or the eczema; at least the improvement which comes from appropriate treatment on a general basis and without regard to allergy is striking. It is interesting to consider that they too have *x* and that this explains why they have one or another of the asthmatic symptoms. They may have abscessed teeth, chronic diseases of the gallbladder or prostate or other evidences of chronic infection. Chronic infectious sinusitis belongs in the category but deserves special considerations because its treatment is so uncertain and hazardous. In many if not most of the cases, the lesions in the sinuses appear to be the result and not the cause of the process. More interesting are the cases of psychic origin. It is better to say that they result from stress and strain. Except for the presenting symptom, the asthma or the eczema perhaps, and the depletion, physical

4. Hyde, R. W., and Kingsley, L. V.: Distribution of Allergic States in Selectees, J. Allergy **14**:386, 1943.

5. Alford, R. I.: The Distribution of Patients with Bronchial Asthma: First Hundred Cases of Bronchial Asthma Admitted to the Percy Jones General Hospital, J. Allergy **25**:196, 1944.

6. French, S. W., and Halpin, L. J.: Army Allergy: Fourth Service Command 1943, Ann. Allergy **2**:365, 1944.

7. Rackemann, F. M.: Allergy: A Review of the Literature of 1943, Arch. Int. Med. **73**:248 (March) 1944.

examination is noncontributory. There is no evidence of allergy. There are several theories to explain this depleted group.

THE ENDOCRINE THEORY TO EXPLAIN DEPLETION

Outwardly and on physical examination, the patients appear normal. Certainly, there is no evidence to suggest hyperthyroidism or hypothyroidism or the excess or the deficiency of any other endocrine gland in the group as a whole. More recently, Harkavy [8] pointed out that in animals anaphylaxis may be inhibited by removal of the thyroid, the parathyroid, the thymus or the testes whereas anaphylaxis may be enhanced by removal of the ovaries, the adrenals or the hypophysis. In human beings, on the other hand, these artificial changes make no difference to the allergy. The cellular reactions are not initiated by the endocrine or the autonomic nervous system. Zondek and Bromberg,[9] in Palestine, made skin tests with various endogenous hormones—estradiol, estrone, progesterone, testosterone and others. In a group of 27 allergic persons they found positive reactions in 19 (70 per cent), whereas similar tests on 32 normal persons elicited no reactions at all. However, 19 patients with pruritus vulvae and acne reacted like the allergic persons in 72 per cent of the cases. There is little so far to support any endocrine theory. Albright [10] objected strenuously to the belief "that anything which is not understood belongs to endocrinology," and I agree. On the other hand, the next section, on the alarm reaction, considers the role of the adrenal, and that is endocrinology.

THE ALARM REACTION

The conception of Selye [11] that the body reacts to stimuli of all sorts in a pattern which is more or less uniform, at least in the qualitative sense, and that this reaction pattern depends on the activity of the adrenal cortex is of considerable interest and may be pertinent to our subject. Selye explained that the first effect of injury is to produce the alarm reaction, the symptoms of which are recognized as varying degrees of surgical shock. The first stage is brief. After it the resis-

8. Harkavy, J.: The Influence of Neuro-Hormonal Regulations on Anaphylaxis and Allergy, J. Mt. Sinai Hosp. **0**:565, 1944.

9. Zondek, B., and Bromberg, Y. M.: Endocrine Allergy, J. Allergy **16**:1, 1945.

10. Albright, F.: Introduction to Diseases of the Ductless Glands, in Cecil, R. L.: Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders Company, 1943, p. 1203.

11. Selye, H.: The Alarm Reaction, in Piersol, G. M., and Bortz, E. L.: Cyclopedia of Medicine, Surgery and Specialty, ed. 2, Philadelphia, F. A. Davis Company, 1940. Selye, H., and Pentz, E. I.: Pathogenetical Correlations Between Periarteritis Nodosa, Renal Hypertension and Rheumatic Lesions, Canad. M. A. J. **49**:264, 1943. Selye, H.; Sylvester, O.; Hall, C. E., and Leblond, C. P.: Hormonal Production of Arthritis, J. A. M. A. **124**:201 (June 22) 1944.

tance rises so that further stimulation of the same sort will no longer produce the same effect. The patient is in the stage of countershock. During the resistant, or countershock stage the symptoms and signs, if any, are those of adrenocortical overdosage, and this if long continued will lead to a variety of lesions, some of which can be recognized in cases of advanced asthma. The pathologic picture called periarteritis nodosa is one. Lesions in the joints with infiltrations of lymphocytes and the production of granulomatous areas is another. A number of separate hormones have been isolated from the adrenal cortex. Desoxycorticosterone is one of these, and when rats are treated by injections of this substance many interesting changes occur. The thymus and the pancreas degenerate, and there may be ulcerations of the gastrointestinal tract; the lungs become hyperemic. Meantime, the temperature falls and the rate of basal metabolism falls, but the blood sugar and the nonprotein nitrogen levels increase. There is dehydration with concentration of the blood, so that the white cell count and the red cell count go up. These effects—and the list here is only partial—are produced in animals under artificial conditions. In the clinic one sees such symptoms as periarteritis nodosa in occasional cases of severe asthma. I recall at least 2 patients with severe asthma in whom a gastric hemorrhage developed from a peptic ulcer. Whereas it is not often possible to recognize the symptoms of the resistant stage of Selye in a patient whose asthma is not severe, nevertheless the whole conception is pertinent to the problem of asthma, and it may well be that when more is known about the functions of the adrenal cortex one can recognize that asthma occurs because of some disturbance of the adrenal mechanism.

Meantime, Albright,[12] in a fascinating lecture on Cushing's syndrome, has presented the theory that during the resistant, or countershock, stage the sugar-regulating mechanism of the adrenal gland (he calls it the S hormone) is produced in great excess, thereby depleting the body, whereas the nitrogen-building factor (the N hormone) is withheld during the stage of countershock. This means that the tissue is broken down at a rapid rate and without attempt at repair.

A patient with severe asthma, a tired business man of 50 years, was seen last year by Dr. Albright in consultation.[13] The man was greatly depleted in body weight and strength. His asthma was severe. The fact that he excreted only 5 mg. of 17-keto steroids in place of a normal excretion of about 15 mg. was taken as evidence that his nitrogen-building adrenal hormone was deficient. He was considered to be in

12. Albright, F.: Cushing's Syndrome, in Harvey Lectures, 1942-1943, Lancaster, Pa., Science Press, 1943, vol. 38, p. 123.

13. Rackemann, F. M.: Medical Progress: New Theories Concerning Asthma, New England J. Med. **230**:284, 1944.

the countershock stage of the alarm reaction, and his severe asthma was considered as a part of that process. Aside from rest in bed and general care of the best sort this man was given injections of testosterone proprionate, and he did well. At the same time, however, patients with a somewhat similar picture had likewise done well simply on the rest in bed and good nursing care, without the extra hormonal treatment. Last winter I [14] described depletion as an important factor in severe asthma and, in doing so, implied that the patient was in the countershock stage of the alarm reaction and that the cause of his trouble was concerned in some way with adrenal disturbances. Meantime, of course, there are patients who have been treated with an adrenal cortex extract (Eschatin) and other commercial preparations of adrenal cortex hormones without success. The theory has been considered before, but it must be considered again. It has opened an immense field for further investigation.

One must recognize, however, that this theory about the alarm reaction and the effect of adrenal hormones is concerned probably more with the effects of the allergic reaction than with the cause of it. The reaction is a response to stimuli, and the allergy produces the stimulus. It is considered here because it may offer a possible explanation for the fact that allergy develops only in certain persons. Perhaps it is that in their cases the symptoms and signs of the alarm reaction develop more promptly and from slighter causes than happens in the cases of normal persons.

Chronic vitamin deficiency must be considered as a cause of depletion. Do the signs and symptoms of asthma or the appearance of allergy per se appear at a certain time because the person is in poor condition because of improper feeding? Vitamin A has been discussed by Clausen,[15] who pointed out that patients with chronic infections are apt to have low levels of plasma vitamin A and that their resistance to infection falls when the vitamin A is depleted. Ascorbic acid is concerned with the production of antibodies. It was thought at one time that large doses of ascorbic acid might do good in hay fever and asthma, but Friedlaender and Feinberg [16] have studied the question, finding that the blood level of vitamin C is normal in hay fever and that treatment with as much as 500 mg. of ascorbic acid daily did no good. Hebald [17] agreed. There is no evidence that ascorbic acid plays any

14. Rackemann, F. M.: Depletion in Asthma, J. Allergy **16**:136, 1945.

15. Clausen, S. W.: Absorption of Vitamin A and Its Storage in Tissues, in Harvey Lectures, 1942-1943, Lancaster, Pa., Science Press, 1943, vol. 38, p. 199.

16. Friedlaender, S., and Feinberg, S. M.: Vitamin C in Hay Fever: Therapy and Blood Levels, J. Allergy **16**:140, 1945.

17. Hebald, S.: Clinical Evaluation of Ascorbic Acid in the Treatment of Hay Fever, J. Allergy **15**:236, 1944.

part in the disease. Incidentally, Rocha e Silva [18] gave large doses (200 to 500 mg.) of ascorbic acid to rabbits before testing for anaphylactic shock and found that the treated animals were no different from the controls; the ascorbic acid had no effect either on the intensity of the shock or on the reduction of the histamine content of the blood after it.

Psychic disturbances can cause queer symptoms. There are occasional cases of asthma in which they are so important as to constitute a rational explanation for all the trouble. Some interesting figures may be quoted here. As said before, Hyde and Kingsley [4] rejected about 1 per cent of draftees on account of asthma and other allergic disorders. In a group of 11,647 patients afflicted with functional psychoses, Leavitt [19] found only 10 patients with asthma, and in another group of 5,000 mentally defective and epileptic persons not one patient with asthma was observed. Dr. Stanley Cobb [20] agreed with Leavitt that the incidence of certain chronic disorders like arthritis and asthma are rare among insane persons, and he explained it this way: When a person becomes anxious and frustrated so that he loses control of his emotions, one of three things, and only one, may happen. First, he may regain control and recover; second, his loss of control may go on to complete psychic deterioration, or, third, his emotional tension may spill over into the development of somatic symptoms, usually of the vasomotor group of disturbances, notably, asthma, urticaria, eczema or arthritis, any one of which can provide an outlet for his emotional suffering. These three directions are quite distinct one from the other. In a patient who goes on to psychic deterioration, vasomotor symptoms do not also develop: insane patients do not have vasomotor disturbances, and they do not have asthma. In the meantime, Zeller and Edem [21] made skin tests by the scratch method with pollen on 372 patients in a hospital for insane persons and found positive reactions in 15, or 4 per cent, and all but 1 of these had clinical hay fever. Allergy was present in a normal proportion, and the symptoms due direct to the allergy developed as usual. It was the extra symptoms, built up on a psychic basis, which were lacking in the insane persons.

This discussion suggests, therefore, that in persons who have inherited the asthmatic state depletion, whether of the soma or of the psyche, may result in asthma or, for that matter, in any other manifestation of the state, such as chronic urticaria or eczema or polypoid sinusitis.

18. Rocha e Silva, M.: Failure of Ascorbic Acid to Influence the Variations of the Histamine Content of Rabbits Blood During Anaphylactic Shock, Rev. brasil. de biol. **3**:39-44, 1943.

19. Leavitt, H. C.: Bronchial Asthma in the Functional Psychoses, Psychosom. Med. **5**:39, 1943.

20. Cobb, S. S.: Personal communication to the author.

21. Zeller, M., and Edem, J. V.: Allergy in the Insane, J. Allergy **14**:564, 1943.

The observations of Selye [11] and Albright [12] suggest that one of the factors in this depletion is a disturbance of the adrenal cortex, but much more information is needed. Here, indeed, is a problem for further study.

What about infections and intoxications? In these two categories there is always the question of selective localization dependent on the function of the bacteria or the drug, but more reasonable is another aspect of allergy. In certain patients sinusitis develops with regularity with each new head cold; other patients will have bronchitis: I have seen chronic atopic eczema flare up with infections, and I have seen urticaria develop in a day or two after a new head cold. One must consider that certain tissues are more susceptible to the bacterial toxin and that this may depend on a specific reaction factor—an antibody—and that means allergy. Here again the reaction pattern remains true to form; the "asthmatic state" is still important.

THE LESION IN ALLERGY

The basic lesion in allergy consists in the capacity to develop sensitiveness. That is the difference between persons who are allergic and those who are normal. Meantime, the allergic reaction with swelling and edema, with the dilatation of small capillaries and the constriction of entering arteries, has been discussed as protective in nature—the purpose being to hold the offending substance at the site of entrance and so prevent it from invading the body. How about the absorption of foreign substances from the gastrointestinal tract of sensitive and nonsensitive persons? Can the protective effect of allergy be demonstrated in this way? Is there any evidence that absorption of the specific substance is inhibited in persons who are sensitive to it? The question has been studied by Hecht and others [22] in Sulzberger's clinic, and with interesting results. The skin of normal persons was sensitized with the serum of a patient highly sensitive to ragweed pollen, and then two days later the person was given, on a fasting stomach, capsules containing 5 Gm. of ragweed pollen. Sixteen of the 22 subjects absorbed enough ragweed to cause a reaction in the passively sensitized skin site. However, the reactions varied, and it was found later that the absorption was influenced by the presence of acid or alkali in the stomach. The administration of acid tended to prevent the absorption, whereas the administration of alkali tended to increase it. The results of this experiment are interesting; the method used is also interesting because it shows how the absorption of foreign protein substances might be studied fairly easily. The results are comparable

22. Hecht, R.; Mosko, M. M.; Lubin, J.; Sulzberger, M. B., and Baer, R. L.: The Absorption of Whole Ragweed Pollen from the Gastro-Intestinal Tract, J. Allergy **5**:9, 1944.

to those obtained previously by Walzer and Golan,[23] who have made extensive studies on the absorption of foreign substances which were administered in considerable variety and by different methods. One would suppose that this general technic ought to be of considerable interest to students of digestion and nutrition.

HISTAMINE

The chart presents the theory that the asthmatic state sets the stage so that the actor will respond with various vasomotor symptoms when prompted in various ways. Allergy is the first and typical way, but depletion, infection and intoxication appear to be other ways if clinical observations can be trusted. The stage plus the prompting makes the patient release H substance. Is this diagram correct? Does the action in each case involve H substance? Does depletion, for example, cause asthma or vasomotor rhinitis because it liberates histamine or changes the reaction toward it? Could H substance have anything to do with Loeffler's syndrome?

First, let me review the points about histamine which are pertinent to this discussion. It was in 1910 that Barger and Dale[24] isolated β-imidazolylethylamine (histamine) from ergot and in 1911 that Barger and Dale[25] found histamine in the intestinal mucosa. Since then its precursor, histidine, has been recognized as a common constituent of body cells. As Best and McHenry[26] stated, it is found especially in all the barrier tissues—the skin and the intestinal mucosa. In 1927, Best, Dale, Dudley and Thorpe[27] showed that the mother substance, histidine, was available in ample quantities and that the antigen-antibody reaction of allergy was capable of removing the carboxyl group to change histidine into histamine in the living animal. Bacterial action also can cause this change.

In a comprehensive review before the American Academy of Allergy in 1944, Dragstedt[28] declared that the release of histamine is at least a major factor in the production of allergic symptoms in man although it is not necessarily the only factor involved. The fact is that whereas

23. Walzer, M.: Absorption of Allergens, J. Allergy **13**:554, 1942. Walzer, A., and Golan, H. G.: The Transport of Antigen Through the Body by Electrophoresis, ibid. **16**:165, 1945.

24. Barger, G., and Dale, H. H.: The Presence in Ergot and Physiological Activity of B-Imidazolethylamine, J. Physiol. **40**:38, 1910.

25. Barger, G., and Dale, H. H.: B-Iminazolylethylamine: A Depressor Constituent of Intestinal Mucosa, J. Physiol. **41**:499, 1911.

26. Best, C. H., and McHenry, E. W.: Histamine, Physiol. Rev. **11**:371, 1931.

27. Best, C. H.; Dale, H. H.; Dudley, H. W., and Thorpe, W. V.: Nature of Vaso-Dilator Constituents of Certain Tissue Extracts, J. Physiol. **62**:397, 1927.

28. Dragstedt, C. A.: The Significance of Histamine in Anaphylaxis and Allergy, Quart. Bull. Northwestern Univ. M. School **17**:102, 1943.

histamine has been isolated from many tissues and identified as such it has not been "caught red handed at the scene of the crime." Sir Thomas Lewis [29] recognized this when he made the first reference to H substance. He wrote, "I shall speak of an 'H.-substance' and in using it shall mean any substance (or substances) that is liberated by the tissue cells and exerts in the minute vessels and nerve endings an influence culminating in the Triple Response."

When most authors discuss histamine what they refer to is the property of the experimental extracts—blood serum, tissue fluid or cell suspension—to produce a characteristic contraction of guinea pig muscle or to produce a fall in the peripheral blood pressure of the cat. To exclude depressor substances other than histamine the experimental fluid must be acidified and boiled, and under these conditions it is most probable that the reactions produced do depend in fact on histamine.

The development of the knowledge of histamine by a long series of experiments has been summarized recently in an excellent review by Code.[30] Recent advances concerning the histamine problem have been described by M. Rocha e Silva.[31] In the blood of animals, Code [32] himself showed that the white cells contained a large amount of histamine while the plasma had little. Later, Code and Ing [33] extracted the active principle from the white cell layer of rabbit blood and identified it as histamine. In the rabbit and under the conditions of that experiment, H substance really was histamine. Leukopenic blood contains less histamine in accordance with the diminished white cell count.

In anaphylactic shock in both guinea pigs and dogs the amount of histamine-like activity in the blood will rise, but, as Code [34] found, this rise is transient and in a few minutes the concentration falls to normal. More important for the theory here are the many experiments which show that histamine-like activity is released from the tissues of animals during the anaphylactic reaction. Katz [35] found that when a solution

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29. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, Ltd., 1927.

30. Code, C. F.: The Mechanism of Anaphylactic and Allergic Reactions: An Evaluation of the Role of Histamine in Their Production, Ann. Allergy **2**:457, 1944.

31. Rocha e Silva, M.: Recent Advances Concerning the Histamine Problem, J. Allergy **15**:399, 1944.

32. Code, C. F.: The Source in Blood of the Histamine-Like Constituent, J. Physiol. **90**:349, 1937; The Histamine-Like Activity of White Blood Cells, ibid. **90**:485, 1937.

33. Code, C. F., and Ing, H. R.: Isolation of Histamine from White Cell Layer of Centrifuged Rabbit Blood, J. Physiol. **90**:501, 1937.

34. Code, C. F.: The Histamine Content of the Blood of Guinea Pigs and Dogs During Anaphylactic Shock, J. Physiol. **127**:78, 1930.

35. Katz, G.: Histamine Release from Blood Cells in Anaphylaxis in Vitro, Science **91**:221, 1940.

of egg white was added to the blood cells of a rabbit sensitized to egg and the mixture was incubated the plasma contained from two to six times as much histamine as did the plasma of the same blood before treatment. Incidentally, he commented on this observation as an indication of a method of study which might be useful in clinical allergy. In the next year Katz and Cohen [36] studied patients with ragweed hay fever and found that the method worked.

When the organs of sensitized animals are removed and then perfused with salt solution to which a quantity of antigen is added, histamine-like activity can be demonstrated in the perfusate. This was found first in 1932 by Bartosch, Feldberg and Nagel.[37] Schild [38] observed that the perfusate from lungs treated with antigen contained histamine activity but that the perfusate from lungs treated with barium chloride, which also caused contraction of the bronchial muscles, did not show it. The histamine activity did not come from the muscle spasm alone. Since then, histamine-like activity has been found by various workers in other organs perfused during and after anaphylaxis. Dragstedt and Mead [39] found it in the lymph of dogs in anaphylactic shock. Meantime, Dragstedt [28] noted that the identification of histamine itself in the blood is always difficult because the quantities are so small. He calculated that a dog weighing 10 Kg. has only 0.75 mg. of histamine in his entire blood stream.

In patients with allergy, Rose [40] has shown that the concentration of blood histamine changes during attacks of asthma and of urticaria. During the first minutes there is in human beings, as in animals, an increase in blood histamine, and later there is a fall. One should note, however, that the relation between the amount of histamine activity in the blood and the symptoms is not so direct as one would like to expect. Whether the discrepancy depends on technic, including the time when the samples were taken, or whether it shows that some other factor is operating at the same time is debatable.

In his evaluation, Code [30] pointed out that there is evidence to suggest that along with histamine other substances, notably heparin, may

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36. Katz, G., and Cohen, S.: Experimental Evidence for Histamine Release in Allergy, J. A. M. A. **117**:1782 (Nov. 22) 1941.

37. Bartosch, R.; Feldberg, W., and Nagel, E.: Das Freiwerden Eines Histaminähnlichen Stoffes bei der Anaphylaxie des Meerschweinehens, Arch. f. d. ges. Physiol. **230**:129, 1932.

38. Schild, H.: Histamine Release and Anaphylactic Shock in Isolated Lungs of Guinea Pigs, Quart. J. Exper. Physiol. **26**:165, 1936.

39. Dragstedt, C. A., and Mead, F. B.: Role of Histamine in Canine Anaphylactic Shock, J. Pharmacol. & Exper. Therap. **57**:419, 1936.

40. Rose, B.: The Relation of Histamine to Anaphylaxis and Allergy, McGill M. J. **10**:2, 1940; Studies on Blood Histamine in Patients with Allergic Disease, J. Clin. Investigation **20**:419, 1941.

be released at the same time. On the whole, however, the histamine theory is plausible. The injection of it into normal animals or human beings can mimic all the symptoms of allergy and anaphylaxis. It offers a reasonable explanation of the fact that a uniform symptom complex can be produced by a variety of exciting causes.

Is there any difference in the degree of reaction which different persons may exhibit toward histamine? In 1933, Rackemann, Simon and Scully [41] compared the skin tests with histamine on 85 asthmatic patients and 23 normal persons (nurses). Serial dilutions up to 1 to 1,000,000 were injected intracutaneously into the arm of each person. The reactions were a trifle larger in the asthmatic group, but the differences were not pronounced. More important is the old observation of Weiss, Robb and Blumgart [42] that patients with asthma are more susceptible to histamine than normal persons. They observed this during a study in which the flush which follows the intravenous injection of histamine was used as an index of the circulation time. In the patients with asthma, the flush appeared sooner and was much more pronounced than in the normal persons. Evidently, then, there is a little evidence than asthmatic persons are more susceptible to histamine than normal persons.

The next problem is to see whether histamine may be the mediating substance in conditions less well defined and which clinically depend on depletion, infection or intoxication. What else beside the antigen-antibody reaction will result in the release of histamine? Anrep and his co-workers [43] have shown that after exercise to produce hyperemia or after compression of the arm by a blood pressure cuff the histamine content of the plasma will increase as much as sixfold. Stead and Warren [44] observed that if histamine is injected into the brachial artery the capillaries of the forearm and hand become permeable, plasma is lost rapidly and venous blood from the area becomes concentrated. It is a temptation to use this last as an argument for the idea that other cholinergic influences can squeeze out histamine. In 1929, Kalk [45] observed

41. Rackemann, F. M.; Simon, F. A., and Scully, M. A.: Further Observations on the Nature of Allergy, J. Allergy **4**:498, 1933.

42. Weiss, S.; Robb, G. P., and Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels, Am. Heart J. **4**:664, 1929.

43. Anrep, G. B.; Barsoum, G. V.; Salama, S., and Souidan, Z.: Liberation of Histamine During Reactive Hyperemia and Muscle Contraction in Man, J. Physiol. **103**:297, 1944.

44. Stead, E. A., and Warren, J. V.: The Effect of the Injection of Histamine into the Brachial Artery on the Permeability of the Capillaries of the Forearm and Hand, J. Clin. Investigation **23**:179, 1944.

45. Kalk, H.: Existence of a Histamine-Like Substance in Dermographism, Klin. Wchnschr. **8**:64, 1929.

that scratching the skin of a patient with dermographia will result in an increase of his gastric acid.

What is needed is a further study of depletion, including "nervous exhaustion" due to stress and strain, to find the mechanism by which these psychosomatic disturbances will produce their symptoms—obviously a complicated and difficult problem. Another paper by Rose [46] indicates the kind of studies which might be useful. He found that adrenalectomized rats could not inactivate histamine but that if the animals were fed adrenal cortex substance as desoxycorticosterone in fair-sized doses the function could be restored. This observation fits well with Selye's conception of the alarm reaction, to encourage the idea of adrenal deficiency as a basic factor. For the moment, it seems fair to allow the upper portion of the diagram in the chart to stand—that is, to assume that a variety of clinical states can result in the liberation of H substance.

Clinical treatment aimed at histamine might if successful provide further evidence that H substance was responsible for the symptoms in patients. Dragstedt [28] quoted Wells as suggesting that if histamine is important desensitization which inhibits one kind of a specific reaction ought to inhibit other reactions in the same animal at the same time. This statement, however, overlooks the fact that desensitization concerns nothing more than the specific antigen-antibody reaction and so merely removes the stimulus by which histamine is liberated. To inhibit histamine two methods have been devised. One concerns histaminase, a ferment to destroy histamine. The other concerns immunization against histamine itself.

In 1930, Best and McHenry [47] found that extracts of fresh tissue, particularly from the small intestine and kidney, could neutralize histamine in the test tube. In guinea pigs, Karady and Browne [48] first expressed the opinion that treatment with this histaminase could protect against anaphylactic shock, but later Rose and Browne [49] could not confirm the findings. In the treatment of patients the so-called histaminase has been found by many workers to be worthless. More recently, Lemley and Laskowski [50] have shown that in doses adequate

46. Rose, B.: The Effect of Cortin and Desoxycorticosterone Acetate on the Ability of the Adrenalectomized Rat to Inactivate Histamine, Am. J. Physiol. **127**:4, 1939.

47. Best, C. H., and McHenry, E. A.: The Inactivation of Histamine, J. Physiol. **70**:349, 1930.

48. Karady, S., and Browne, J. S. L.: Effect of Histaminase Treatment on Histamine and Anaphylactic Shock in Guinea Pigs, J. Immunol. **37**:463, 1939.

49. Rose, B., and Browne, J. S. L.: Effect of Histaminase Pretreatment on Histamine Shock in Guinea Pigs, J. Immunol. **41**:409, 1941.

50. Lemley, J. M., and Laskowski, M.: The Action of Histaminase in Vivo, Arch. Biochem. **6**:115, 1945.

to produce a real effect the material is highly toxic. If some new substance of that kind could be discovered, perhaps on a different principle, that would be wonderful.

Immunization against histamine itself by repeated injections of it are not effective. Several papers on the subject were noted in the review of the literature on allergy for 1943.[7] Histamine is like its antagonist epinephrine—a substance which is present in the body normally and which has a well marked physiologic action. Is it surprising that a change in its quantity or in the resistance to its effects is hard to bring about? An exception to this sentiment is the result which Horton and his co-workers [51] have obtained in the special type of headache which they called "histaminic cephalalgia." Horton found that when histamine is well diluted with isotonic solution of sodium chloride and then injected intravenously at a rate of injection which keeps the dose just below the reaction level the results are good—almost spectacular in many cases. Whether this disease, which appears to be a local vascular disturbance due to a sort of intolerance to histamine, can be considered as comparable to the other, more typical, "asthmatic" symptoms remains to be seen. The physiology of histamine is complicated. Disturbances of the normal mechanism can be expected. Our knowledge of them is meager.

Histamine-protein combinations made by an azo linkage were first devised in 1943 by Fell, Rodney and Marshall,[52] who hoped to produce an immunity by the special preparation which they made. The new substance was found to be antigenic, so that in animals immunized to it precipitins of a typical sort developed. When, however, the serum from a rabbit immunized with histamine-azo-horse-serum was tested against histamine-azo-rabbit-serum or histamine-azo-casein, the reactions were not entirely clearcut. The specific element of the foreign serum was plainly evident, for the serum reacted better with the same material which had been used for immunization, but it reacted also with the other substances and that indicated that the histamine itself retained a function as a hapten. Animals immunized with these new substances did not lose any immediate histamine from their peripheral blood. They did, however, become resistant to anaphylactic shock, and the authors concluded that the previous treatment had resulted in an inhibition of the histamine and so caused their resistance to

51. Horton, B. T.; MacAen, A. R., and Craig, W. M.: A New Syndrome of Vascular Headache: Results of Treatment with Histamine; Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**:257, 1939. Horton, B. T.: The Use of Histamine in the Treatment of Specific Types of Headaches, J. A. M. A. **116**:377 (Feb. 1) 1941.

52. Fell, N.; Rodney, G., and Marshall, D. E.: Histamine-Protein Complexes Synthesis and Immunologic Investigation: I. Histamine-Azoprotein, J. Immunol. **47**:237, 1943.

anaphylaxis. In another experiment by Rodney and Fell,[53] the isocyanate derivative of histamine was coupled with despeciated horse serum globulin, and in this experiment again were a number of cross reactions easily demonstrated. This substance also could protect guinea pigs against the symptoms of anaphylaxis when they were immunized to it. The protection, however, was not perfect.

Cohen and Friedman[54] prepared histamine-azo-despeciated-horse-serum according to Fell's method and treated a number of patients with it, giving doses three to seven days apart for as long as three to twelve months. Precipitins to the injected complex were demonstrable at the end of treatment. When histamine was added to the precipitating serum and the mixture incubated for a time, the addition of the antigen complex no longer produced a precipitin reaction, for precipitin had been absorbed by the histamine. Moreover, when mixtures of serum from treated patients and histamine were applied to the skin of a normal subject and then tested with an electric current to drive the material in by the process of iontophoresis, no cutaneous reactions occurred. The histamine had been neutralized. In another paper, Cohen and Friedman[55] showed that the treatment of patients suffering from urticaria, allergic rhinitis and intrinsic asthma with histamine-azo-protein resulted in a diminution of their sensitiveness to histamine as applied by skin tests.

Meantime, M. Rocha e Silva[56] made five different compounds of histamine with amino acid and showed that when tested on the blood pressure of cats, guinea pig intestine or human skin there was little if any pharmacologic activity; the histamine had been bound or captured by the compound. When later the compound was hydrolized in the presence of acid, the histamine was liberated so that the mixture would once more show its characteristic effects. Landau and Gay[57] added arginine and histidine to the Dale Bath and so prevented the reaction of the strip of guinea pig muscle to histamine. Also they showed that an injection of arginine can protect a guinea pig against an otherwise

53. Rodney, G., and Fell, N.: Histamine-Protein Complexes: Synthesis and Immunologic Investigation: II. B-(5-Imidazolyl Ethyl Carbamido Protein, J. Immunol. **47**:251, 1943.

54. Cohen, M. B., and Friedman, H. J.: Antibodies to Histamine Induced in Human Beings by Histamine Conjugates, J. Allergy **14**:195, 1943.

55. Cohen, M. B., and Friedman, H. J.: Immunity Against H-Substance, J. Allergy **15**:245, 1944.

56. Rocha e Silva, M.: Pharmacological Properties of Simple Compounds of Histamine with Amino Acids, J. Pharmacol. & Exper. Therap. **77**:198, 1943.

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lethal dose of histamine, but it cannot protect the sensitized animal against death from anaphylactic shock.

More recently, Lehmann and Young [58] have recognized the antihistamine activity of diethylaminoethyldihydroanthracene carboxylate and showed that the injection of it can protect animals against anaphylactic shock with egg white. Also it can reduce the cutaneous reaction to histamine, and it can reduce the volume though not the acid concentration of the gastric juice when histamine is injected.

As for acetylcholine, the pharmacologic effect is much like that of histamine, but the fact that atropine, which is so effective in preventing the action of acetylcholine in animals, has no effect on the symptoms of allergy in human beings has been in itself a strong argument against the theory that acetylcholine plays an important part in allergy. Farber with Pope and Landsteiner [59] made a direct experiment; they removed the hearts, lungs and small bowels from normal guinea pigs and from other pigs sensitized to horse serum and divided each organ into two parts. One part was placed in plain Ringer's solution, while the other was placed in Ringer's solution to which physostigmine salicylate had been added. When horse serum was added to these mixtures, one might expect that acetylcholine as well as histamine would be released in each part of each preparation. In the part containing physostigmine salicylate, the cholinesterase would be inhibited so that the acetylcholine could be recognized by its typical physiologic effect on smooth muscle. The differences in the effects of the two parts with and without physostigmine salicylate would be a measure of the concentration of acetylcholine. In the actual experiment there was no evidence to indicate that more acetylcholine was released from the sensitized tissue than from the normal tissue. Meantime, in another experiment with the same sensitized tissues, the addition of specific serum resulted in the release of histamine, which was easily recognized in all preparations. More study of the histamine problem is needed. So far one can say that histamine appears to be a common denominator important in production of asthmatic symptoms, whether these are excited by allergic reactions or by other factors. The theory—particularly concerning these "other" factors—is not yet secure. The search for a treatment based on the histamine theory which will cure all the asthmatic symptoms at once is as difficult as it is exciting.

So far the best and most striking "treatment" of allergic diseases is that which occurs naturally or sometimes artificially in the form of

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58. Lehmann, G., and Young, J. W.: The Anti-Histamine Activity of Diethylaminoethyldihydroanthracine-Carboxylate and Other Substances, J. Pharmacol. & Exper. Therap. **83**:90, 1945.

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fever. Fever relieves asthma while the temperature is elevated and often for some time after. Surgical operations relieve temporarily. Jaundice relieves asthma while the jaundice is still present and for some time afterward. Incidentally, in a recent paper Aikawa [60] pointed out that jaundice can also relieve the pain of arthritis. How shall these effects be explained? Are they concerned with the antigen-antibody reaction or with the liberation of H substance, or do these drastic circumstances result in an exhaustion of some other factor essential to the production of symptoms? Are they related to the old observation of Manwaring [61] and others that the liver is an important organ in anaphylaxis and that exclusion of the liver by an Eck fistula can prevent anaphylaxis in sensitized dogs?

Individual symptoms will now be considered to see what is new about them and what problems they present.

263 Beacon Street.

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61. Manwaring, W. H.: Intestinal and Hepatic Reactions in Anaphylaxis, J. A. M. A. **77**:849 (Sept. 10) 1921.

(To Be Concluded)

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